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CONTENTS OF PREVIOUS NUMBER

JUNE 1946. NUMBER 6

Surgical Treatment of Otosclerosis: A Preliminary Report on an Improved Fenestration Technic. George E. Shambaugh Jr., M.D., and Arthur L. Juers, M.D., Chicago.

Late Secondary Tonsillar Hemorrhage: II. Studies of Ascorbic Acid. Harry Neivert, M.D., New York; Leo A. Pirk, Ph.D., Nutley, N. J., and Recha Engelberg, Ph.D., New York.

Treatment of Tuberculosis of the Larynx: An Evaluation. William F. Hulse, M.D., Cleveland.

Penicillin Ear Drops in the Treatment of Suppurative Otitis Media. Lieutenant Colonel William J. Loeb, Medical Corps, Army of the United States.

Hypertrophy of the Masseter Muscle. Major Joseph H. Hersh, Medical Corps, Army of the United States.

Evaluation of Benadryl as a Therapeutic Agent for Vasomotor and Allergic Rhinitis. E. A. Thacker, M.D., Urbana, Ill.

Treatment of Chronic Purulent Otitis Media with Glycerite of Hydrogen Peroxide. Ethan Allan Brown, M.R.C.S. (Lond.), L.R.C.P. (Eng.), Boston, and Walter E. Owen, M.D., Peoria, Ill.

Atresia of the External Auditory Canal Occurring in Military Service: A Report on the Correction of This Condition in Ten Cases. John J. Conley, M.D., New York.

Effect of Zephiran Chloride, Tyrothricin, Penicillin and Streptomycin on Ciliary Action. G. Greenwood, M.D.; R. E. Pittenger, M.D.; G. A. Constant, M.S., M.B., and A. C. Ivy, Ph.D., M.D., Chicago.

Case Reports:

Removal of a Tortilla from the Esophagus. D. Bernstein, M.D., Brooklyn.

Progress in Otolaryngology. Summaries of the Bibliographic Material Available in the Field of Otolaryngology:

Advances in the Understanding of Rhinologic and Otologic Conditions Related to the Nervous System: A Critical Survey of the Literature (To Be Concluded). Wells P. Eagleton, M.D., Sc.D., Newark, N. J.

News and Comment.

Abstracts from Current Literature.

Directory of Otolaryngologic Societies.

General Index.

ARCHIVES OF OTOLARYNGOLOGY

VOLUME 44 JULY 1946 NUMBER 1

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SELECTION OF HEARING AIDS

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AURAL REHABILITATION, MEDICAL ADMINISTRATIVE CORPS

I

SINCE April 1943 the Army Service Forces have been engaged in rehabilitation of soldiers with aural handicaps. At present this rehabilitation is being carried on at the following three centers: Deshon General Hospital, Borden General Hospital and Hoff General Hospital. Each center has been in operation for well over a year. Each has a program combining lip-reading instruction, fitting of hearing aids, auricular (or acoustic) training, speech correction and psychologic guidance.

It has been the responsibility of the three centers to develop and improve their procedures with the view of giving each patient maximum aural rehabilitation. Since the task has called for pioneering, each center has evolved procedures somewhat different from those of the other centers. Furthermore, each center is currently engaged in extending and refining its services.

The present paper is a report on the procedures employed in the selection of hearing aids at Deshon General Hospital. The present report is being made because it summarizes a system which has evolved in the face of clinical necessity. It has proved practical in a hospital situation in which the individual needs of many patients have to be met. It has been effective in selecting for each patient a hearing aid meeting his particular requirements. A report on these methods may therefore prove stimulating to those in civilian life who are engaged in the fitting of hearing aids.

II

The program for the selection of hearing aids at Deshon General Hospital has three goals. These are:

1. To secure for each man a hearing aid having optimal efficiency in everyday situations.
2. To give the man an understanding of hearing aids, establish habits of efficient use, and initiate auricular training.
3. To foster in the patient a full psychologic acceptance of hearing aids.

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III

The hearing aid program at Deshon General Hospital currently consists of several steps.

A thorough analysis is first made of the patient's auditory disability. This includes (1) medical examination and diagnosis, (2) determination of hearing loss and (3) measurement of ability in auditory discrimination. Following the preliminary analysis, a decision is reached as to the general type of fitting best suited to the patient (i. e., whether an air or a bone conduction aid is needed, which ear is to be fitted, and whether special initial training or precautions are necessary). If an air conduction hearing aid is indicated, an individual plastic ear piece is manufactured for the patient. The patient next undergoes a second audiometric study. This study is made to check and confirm the preliminary analysis. Occasional modifications of decision are made necessary at this point.

The patient is next scheduled for an instructional group interview. Here the patient is familiarized with the procedures which will follow. He is introduced to the criteria which he will be expected to employ for rating hearing aids as to performance. Finally, his individual ear piece is tried in his ear to be certain that it is snug and comfortable.

The patient is now ready for the process of selecting a hearing aid. This process involves successive eliminations of less promising instruments and culminates in the finding of the instrument best for the patient. It involves three main stages: The first stage is the elimination of each fitting which is obviously undesirable for the patient and the reduction of the fittings to be given further trial to a practical number. This is accomplished in an individual interview with a trained technician, who selects the fittings to be retained on the basis of the information gathered previously and on the basis of the patient's responses to actual trial of the various hearing aid combinations. In the second stage the patient puts each of the fittings recommended for him to everyday use. He wears each hearing aid for twenty-four hours. At the end of this time he rates the instrument's performance in bringing him thirteen different kinds of sound. These items are controlled reproductions which are presented to the patient in a special session known as the "listening hour." When the patient has put all the recommended fittings through this procedure, the three hearing aid combinations which rate highest are designated for further study. The remaining fittings are eliminated.

The patient then moves on to the final stage, in which the instruments surviving the second stage are put through the "hearing aid evaluation test." This test is a controlled comparison of the instruments while they are worn by the patient. Each aid is measured on sensitivity, limits of tolerance, performance in noise and word discrimination. The instrument best suited to the patient is selected on the basis of the results

of this evaluation test, with some consideration being given to the patient's experiences while using the hearing aids. This instrument is issued to the patient. The patient then embarks on a program of auricular training with his own instrument. If indicated, there also is planned use of the hearing aid in other phases of the rehabilitation program.

The steps preliminary to the actual selection of hearing aids are completed as rapidly as feasible.

The three stages in the selection proper take from seven to fifteen days. This time schedule is purposely maintained in order to incorporate orientational training in the use of hearing aids before the final choice is made. A second purpose is to lay the foundation for further auricular instruction. Clinical experience has led to the firm conviction that the patient whose auditory defect is of long standing needs sufficient time and experience with hearing aids to counteract his old and faulty habits of hearing. Only after these faulty standards have been broken can selection be trustworthy.

IV

With the foregoing summary in mind, the details may now be discussed more meaningfully.

Step 1.—The preliminary analysis of the patient's auditory handicap includes otologic study and hearing tests.

A. Complete otologic examination is obviously essential to discover points requiring special medical consideration and to ascertain whether medical treatment is indicated. Plans to supply a hearing aid to a patient are justifiable only after it is definitely established that medical treatment cannot be expected to remove the hearing deficiency and that there is nothing in the medical picture which makes a hearing aid unsafe. At Deshon General Hospital the medical officers conduct this examination before any audiometric tests are administered.

B. The audiometric survey covers three phases: a pure tone test of air conduction, a pure tone test of bone conduction, and a determination of binaural loss for speech.

In pure tone testing at Deshon General Hospital the procedures advocated by Hughson and Westlake are followed rigorously. They are reported in the manual on rehabilitation of aural casualties prepared for the Committee on Conservation of Hearing and published as a supplement to the *Transactions of the American Academy of Ophthalmology and Otolaryngology*.[1]

Binaural loss in ability to hear speech is determined with equated word lists or, if the patient's linguistic ability is limited, with a specially

1. Hughson, W., and Westlake, H. D.: Manual for Program Outline for Rehabilitation of Aural Casualties Both Military and Civilian, Tr. Am. Acad. Ophth., 1944, supp.

prepared series of simple questions covering Army experiences. The procedure is a modification of the Hughson and Thompson technic for determining threshold of speech reception.[2] Test material is presented by live voice, at a carefully monitored level, through an amplifier and attenuator system connected to high fidelity head phones. The patient, sitting in a sound-treated chamber, wears the head phones and repeats what he hears. A talk-back system allows the tester, who is in a separate talking booth, to hear the patient's responses. The tester manipulates the attenuator and thus controls the intensity of the speech reaching the patient's ears. The tester starts at a level at which the patient repeats readily and then reduces the intensity by large steps

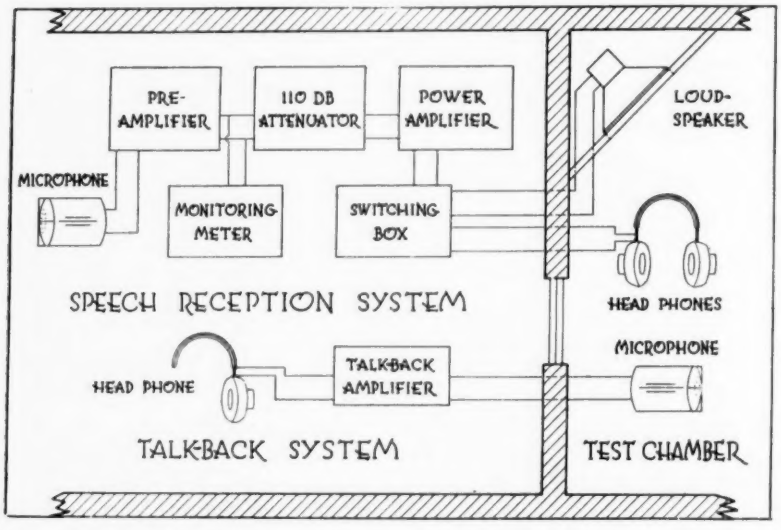

Fig. 1.—Assembly used in testing for the threshold of speech reception.

until the patient's responses indicate that he is close to threshold. The intensity is then varied by smaller steps until a level is reached at which the patient can repeat correctly a little more than 50 per cent of the test items. This level is taken as the threshold of speech reception —and the difference (in decibels) between it and the threshold for persons with normal hearing is the patient's "loss for speech." Incidentally, in determining loss for speech a loud-speaker is sometimes used instead of head phones. When this is done, the patient is seated at a fixed and previously calibrated point in the test chamber. Figure 1 illustrates schematically the arrangements described here.

2. Hughson, W., and Thompson, E.: Correlation of Hearing Acuity for Speech with Discrete Frequency Audiograms, Arch. Otolaryng. **36**:526-540 (Oct.) 1942.

Experience has shown that, with adequate testing material and proper precautions to maintain controlled conditions, the speech reception threshold can be repeated with as great clinical accuracy as can pure tone thresholds. Further, experience and experimentation have led the group at Deshon General Hospital to the firm conviction that *loss in ability to hear speech is an essential datum which must be obtained with every audiometric test.* It has been amply demonstrated that while in the statistical abstract there is a definite interdependence between the threshold of speech reception and the pure tone audiogram, the latter sometimes fails to give an accurate picture of a patient's difficulty in hearing speech.[3] As a generalization, the speech reception threshold and the average of the best thresholds in the band from 512 to 2048 cycles per second show a coefficient of correlation which is approximately + 0.75. Furthermore, the loss in terms of this pure tone average usually is roughly equal to the loss for speech reception.[4] However, some patients show marked differences in threshold according to the two types of test. In extreme cases the loss for pure tones may be 40 decibels less or 30 decibels greater than the loss for speech. In fact, almost one third of all patients show differences of 11 decibels or more. In view of the general linearity between pure tone and speech thresholds, the magnitude of many individual deviations indicates that some patients are handicapped in hearing speech to a greater or lesser degree than they are in hearing pure tones.[5] *The only way to evaluate the significance of the patient's hearing loss is, therefore, to obtain both measures.* This is routine practice at Deshon General Hospital.

When there is discrepancy between the two types of threshold, the loss for speech is usually a better indication of the handicapping effect of the hearing deficiency than is the audiogram. Certainly, decisions regarding future procedures are simplified by considering the relation between the two measures. Typical examples will illustrate the implications. One patient's audiogram may show a pure tone loss averaging about 30 decibels; yet he may have a 55 decibel loss for speech reception. On the basis of the audiogram alone this patient would be considered borderline—with only occasional need for a hearing aid. The loss for speech, however, indicates that the patient should undergo a full hearing aid program, since it is quite probable that an instrument will give him marked practical help. By contrast, if the measures are reversed,

3. Subsequent papers will report the statistical and clinical details which form the basis for this statement.

4. Hughson and Thompson compared average loss from 512 to 2048 cycles per second with loss for speech as measured by the Bell Telephone Intelligibility Lists. They found the two losses to be proportional.

5. Individual study of the cases showing extreme discrepancies has given confirmation of this conclusion.

the interpretation also must be reversed. In other words, although the audiogram would now suggest definite need for a hearing aid, the patient probably has little practical use for one. The validity of this judgment, of course, must be checked by conferring with the patient and by additional tests. From the foregoing illustration it should be clear that the two types of measures give a fuller picture of the patient's need for a hearing aid than either measure alone would give.

The combined measures also carry important implications regarding the strength of the instruments which will serve a patient best. Loss for speech helps determine the practical handicap of the patient's loss of hearing and the power he will need in a hearing aid. Thus, if the pure tone thresholds are at the 85 decibel level while the speech reception threshold is at 60 decibels, the patient probably should be fitted with hearing aids which are less powerful than the audiogram would suggest. In reversed relations the converse follows.

What has just been said does not mean that the pure tone audiogram is unimportant in interpreting the hearing loss or in fitting hearing aids. It reveals the pattern of loss and indicates the type of frequency response which should be favored when hearing aids are selected.

C. As a third facet of the preliminary exploration made in step 1, each patient's ability to discriminate words and syllables in speech is tested. The test is of the "write-down and multiple choice" type. It is one devised at this hospital to give a general picture of discriminative ability and also to isolate the speech sounds causing the patient's particular difficulty. Hence the results are valuable both in giving supplemental information as to hearing aid needs and in pointing to the emphasis which auricular training should take. Incidentally, the test is in several parts. One part is administered to unaided ears—giving an estimate of the difficulty in discrimination which the patient has been experiencing in everyday listening situations. The other two parts are presented through a high quality amplifying system to an ear phone which the patient wears. One of these two parts is presented to the right ear; the other, to the left. Here the results give an estimate of the improvement which can be had with a hearing aid and of special training procedures which are indicated to increase efficient use of an instrument.

Step 2.—A conference is held with the patient. His hearing problems are discussed, and a decision is made as to the general type of fitting best suited to his requirements.

The information gathered in step 1 is of primary importance in this conference. The interview is directed to any special problems of adjustment or hearing need which might affect the patient's program. At this stage the interviewer—who obviously must have wide training and experience—decides whether the patient is to be fitted with an air or

a bone conduction instrument (or whether both types are to be tried). The ear on which the aid is to be worn is selected—or, if the case warrants, a binaural fitting is specified. Instructions regarding special precautions (i. e., tolerance difficulties, and others) are prepared for the guidance of the staff in future steps of the hearing aid program. When the patient requires preliminary auricular training before hearing aids are tried, this is specified. Special tests may be ordered, and in borderline cases further audiometric exploration is directed. Furthermore, during the interview, careful attention goes toward orienting the patient to the steps which will follow. The patient's hearing loss and the practical handicap it presents are discussed realistically. The patient is told approximately what help he may expect from a hearing aid and what special problems, if any, he faces. A patient with mild loss is scheduled for the remainder of the program with the definite understanding on his part that no decision as to whether he will receive an instrument will be made until he has had sufficient experience with hearing aids to reveal to all concerned their practical value for him. Every effort is made to give the patient a feeling of the staff's cooperative interest in reaching decisions which will be of maximum benefit to him.

Step 3.—If the patient is to use air conduction instruments, formal trial of hearing aids does not begin until he has his own individual ear piece. This procedure is imperative because the fit of the ear mold can have such a marked effect on the function of the hearing aid. The performance of instruments with a stock, or "universal," ear piece is often very different from their performance with the patient's own ear piece.

Ear mold impressions are therefore made as soon as possible. These impressions are currently being taken with Impression AC, a methylmethacrylate compound which gives a rubbery and pliable model. This material has proved more practical than plaster when large numbers of patients are being dealt with. It is easily handled, rapid, safer than plaster, and less exacting in regard to the technic required. However, the impression must be processed immediately to avoid shrinkage.

Acrylic ear pieces are immediately manufactured from the impressions. This work is done in a special laboratory maintained in connection with the aural rehabilitation program. This laboratory gives several advantages. Not only are the ear pieces obtained quickly, but the details of manufacture can be checked carefully. As a result the ear pieces fit more snugly, and, when necessary, corrections can be made rapidly.

At Deshon General Hospital it is the practice to make ear pieces for both of a patient's ears whenever there is any possibility that a second might be of value. With both ear pieces available, one can try without delay binaural fitting or shift to the other ear if reception is poor through the ear initially selected for use with hearing aids.

Step 4.—A second audiometric analysis is made as a recheck of the findings of step 1. The recheck includes pure tone loss by air conduction, pure tone loss by bone conduction and binaural loss in reception of speech. These second tests add important information. They either confirm or modify the findings of the first series. Whichever is the case, the technician who will do the preliminary screening (step 6) has available data which will be useful in selecting the most promising instruments for the patient. Furthermore, the second check sometimes reveals special problems which must be explored further in the best interests of the patient.

Step 5.—An instructional interview is held in order that a final orientation may be achieved before the patient has concentrated contact with hearing aids. For this interview, patients are met in groups of 2 to 4.

The patient is not called in until his ear piece is ready. One task in the conference is to try the ear piece to assure that it fits satisfactorily and that hearing aid receivers can be affixed snugly to it. If any difficulties are encountered, the ear piece is immediately sent back to the ear mold laboratory for modification. Thus, a good ear piece is assured for step 6.

A second task in the orientational conference is to make clear to patients the steps which will follow. This is done partly by explaining these steps and partly by staging a practical demonstration of step 8—the listening hour. The patient hears six samples of sound, including instrumental music, a familiar song, an unfamiliar song, recorded speech, sharp noises and a sound discrimination test. These selections are presented through a group hearing aid. Patients are told how to evaluate the reception of each item and are instructed in the use of the rating system employed in the listening hour. Patients also learn what additional items they will encounter in the listening hour.

Finally, the purposes of the whole hearing aid program are reviewed for the patients. Here the aim is to increase the patient's rapport and build an attitude of reserved judgment and of impartial exploration of the various hearing aids. Particular emphasis is given to the description of step 6, which follows immediately.

Step 6.—The first stage in the actual selection of an instrument is a preliminary screening to eliminate unsuitable hearing aid combinations. This is done through an individual interview between the patient and a technician trained in selection of hearing aids. The technician chooses, from the leading makes and models of hearing aids, those combinations which are promising for the patient. In doing so the technician uses several bases for selection.

First the technician selects those combinations of transmitter, receiver and battery which theoretically compensate best for the patient's hearing

deficiency. These theoretic choices are made on the basis of the data gathered in the earlier steps and the decisions made in step 2.

The audiogram is particularly important here, since the aim is to pick instruments which compensate for the pattern of hearing loss. In making judgments, careful cognizance is taken of the recommendations made by each hearing aid company on methods of fitting its own models. However, departures from these recommendations are made in a few instances in which experience at Deshon General Hospital has indicated the wisdom of doing so. Furthermore, the technician takes cognizance of any discrepancy between pure tone and speech reception thresholds.

The technician next has the patient actually try the combinations which have been selected. The patient uses his own ear piece for this. The technician has at his elbow a sufficient stock of transmitters and receivers so that all combinations he may need are immediately available. In practice, each theoretically superior fitting and—in addition—several alternative fittings of each make are tried. Obviously, limitations of time make it unfeasible to try with each patient all possible combinations of instruments. A wide enough sampling is made, however, to check the efficiency of theoretically superior combinations against those representing deviations in various directions from the theoretic. This check is empiric. When the patient puts on an instrument, the technician makes the preliminary adjustments while talking to the patient and getting his reactions. Speech discrimination may be tested informally with selected words and syllables. The technician then makes a judgment on the value of each instrument for the patient. This judgment is not equivalent to patient preference. Rather it is a prognostic estimate made by the technician. The estimate is based on the character and the precision of the patient's response—with appropriate recognition of the patient's preference as a supplementary qualitative datum.

The series of fittings selected for the patient usually include from seven to ten instruments. However, in special cases of extreme loss, only three or four instruments may show any promise. By contrast, when both air and bone conduction types are promising, as many as thirteen or fourteen may be selected. Generally, at least one fitting of each make is included.[6]

At the end of the interview the details of the procedures in steps 7 and 8 are reviewed for the patient. He is then taken by the technician to the "hearing aid library." Here one of the combinations chosen during the interview is assembled and issued on loan to the patient. The patient is thus embarked on step 7. Incidentally, the technician leaves at the hearing aid library the complete list of combinations

6. At present nine makes of hearing aids are being used at Deshon General Hospital.

selected. Thus, the exact fittings may subsequently be loaned to the patient.

Step 7.—In this step, known as the "trial use period," the patient puts to everyday test all combinations recommended for him. He obtains these fittings, one at a time, from the hearing aid library—which has a stock of over 200 instruments. The library personnel follows rigorously the recommendations made in step 6—supplying the patient with the exact combinations specified. Care is taken to insure that each instrument is in good working condition.

The patient keeps each instrument for at least twenty-four hours. He uses it in his everyday activities: in classes, at movies, in the ward, at mess and on pass. At the end of this period he tries the instrument in "listening hour," which will be described under step 8.

An important contribution of step 7 is one of indoctrination and acclimatization to hearing aids. A patient who has never before used hearing aids is at first somewhat at a loss to know what to expect. He is not familiar with the limitations of present day hearing aids. He may be disturbed by the fainter sounds of everyday life, to which his hearing loss has made him unaccustomed. He has to develop skill in judging auditory situations and facility in manipulating hearing aids to meet these situations. Furthermore, if the patient is going to have any special difficulties with hearing aids, the trial use period gives time for his problems to emerge. These problems can then be coped with before a final instrument is supplied. Other prime contributions of the trial use period are those of the crystallization of the patient's realization of his need for a hearing aid, the implantation of a clear concept of exactly what help he may expect from or[illegible] development of an attitude of impartially evaluating all instruments with the view of finding the one most efficient for him. With these attitudes established, the patient will be a more effective user of his hearing aid.

The trial use of hearing aids also gives, as does the listening hour, preliminary auricular training. By virtue of the fact that the patient is wearing various instruments with the intention of finding the flaws and the strength of each, he listens critically and discriminately. This develops awareness of auditory differences and lays the foundation for more rigorous training when the patient receives his own instrument. The whole process is facilitated by the listening hour, which—because of the materials it includes—serves both training and screening functions.

Step 8.—This step is known as the listening hour. It is a group activity, which is carried on with as many as 25 or 30 patients at one time. Here various everyday sound experiences are reproduced at levels similar to those encountered in life. Some of the sound samples are presented from phonograph records through a good quality loud-speaker system. Other samples are presented by live voice. An effort is made

to maintain approximately equivalent intensity levels from one listening hour to another—but this is not critical since (1) all samples are presented at medium levels and (2) the patient is free to adjust each instrument for best reception of each sample. Every item in the listening hour is presented long enough to allow the patient to make necessary adjustments and to judge the excellence of reception with the hearing aid. The usual time per sample is from one minute to a minute and a half.

A patient attends one listening hour program a day. Here he rates the instrument he has been trying during the preceding twenty-four hours. The number of sessions in which he takes part depends on the number of instruments specified in step 6. Throughout the series the patient always sits in the same place in the room and always has live voice material presented by the same staff member.

The repertoire of sound samples used in the listening hour includes six musical selections, speech under three conditions and sharp noises.

The six musical selections are as follows:

1. Instrumental music ("The Blue Danube" played by the Minneapolis Symphony Orchestra)
2. Familiar song—male voice ("Wanting You" sung by Nelson Eddy)
3. Familiar song—female voice ("Old Folks at Home" sung by Veronica Wiggins)
4. Unfamiliar song ("Kerry Dance" sung by Jeanette McDonald)
5. Musical comedy—female ("I Can't Say No," from "Oklahoma")
6. Musical comedy—male ("Kansas City," from "Oklahoma")

The three conditions for speech reception are:

1. Moderate intensity reading of prose in quiet
2. Moderate intensity reading of prose against background music ("Blackberry Polka")
3. Recorded speech (selection by Lynn Fontaine from "The White Cliffs of Dover")

Several strong environmental noises are presented from commercial sound effects records. These noises are presented at moderately intense levels—as they would be if the person were at least several yards from the source. The noises employed are:

1. Tractor
2. Planing mill
3. Buzz saw
4. Ships bells
5. Chinese gong

Incidentally, sharp noises are presented at the end of the listening hour. This is done because some men find that such noises increase tinnitus and interfere with other items in the hour.

Another item of the listening hour is a localization test. There are strong theoretic reasons for questioning the value of a localization test

in rating hearing aids. Patients, however, often report subjective differences, and the results of the listening hour do show statistically significant variations in relation to this item. A localization check is therefore included. The technic of this test is simple. Each patient is assigned a different number. The directing staff member calls out a number and then asks a question. The man whose number is called answers the question. All men have their eyes closed and each judges the direction from which the answer came. The person who answered is then pointed out to the group. This procedure is repeated several times.

Several sound discrimination tests have been employed as part of the listening hour. The purpose of these tests is to measure the precision with which auditory difference can be picked up with the hearing aid. Confusions are more easily made with some instruments than with others. At the present time a special "write down" type word test is being used at Deshon General Hospital. It is hoped that before long this test will be available for general distribution. A substitute test for illiterate subjects involves saying whole sentences, some of which contain predetermined sound substitutions. The patient indicates by a single mark those sentences in which he hears substitutions.

As a supplement to the listening hour procedure, each patient is required to check telephone reception through each hearing aid. During the listening hour he reports his experience.

As the repertoire of sound samples is presented, the patient judges the hearing aid on the excellence of reception with each sample. (The discrimination test is scored on the number of correct responses.) The patient codifies his judgment on a five point scale by indicating on a printed form whether the reception is excellent, very good, good, fair or poor. His judgments are transformed into numerical values by the staff member—who assigns the following values: excellent, 5; very good, 4; good, 3; fair, 2; poor, 1.

A final score is computed for each hearing aid tried. To obtain this score the ratings on all items except the discrimination test are totaled. To this result is added a weighed value representing the score on the discrimination test. The combined total is the final score for the hearing aid. Incidentally, in arriving at this total, double value is given to reception of reading in noise and triple value to reception in the presence of sharp noises.

As supplementary information, the patient is asked for a rating on each instrument's performance outside listening hours. These ratings are not included in computing the final listening hour scores, but they facilitate judging any instrument's usefulness for the patient.

The same process is repeated for every instrument specified for the patient.

After all instruments have been tried, the patient is asked to select in rank order the three he judges most satisfactory. As a matter of interest these ratings are compared with the listening hour scores.

Statistical analyses of listening hour scores indicate that the method is highly discriminative between instruments—particularly in terms of weeding out the less desirable ones. For example, analysis of variance revealed with high significance that some makes of instruments yield statistically better listening hour scores than other makes. Of the nine brands studied, four stood out as particularly good and three were definitely inferior as judged in the listening hour. This was true as to the total listening hour score and as to scores on most of the individual items. Again, analysis of variance gave very significant differences both on total scores and on scores of all individual items when aids were grouped according to patient preference. Here, *t* tests showed that first choice instruments had total scores which exceeded with a significance well beyond 1 per cent the scores of second choice instruments, the second choice exceeded the third choice with 5 per cent significance, and the third choice exceeded instruments not preferred by considerably more than 1 per cent. Similar relations held in general for separate items—but with reduced significance in some instances.

As used at Deshon General Hospital, the listening hour is made the screening device for selecting the instruments to be given final exhaustive tests. However, it also serves as a means of auricular training. This has already been discussed. It is apparent that the listening hour —by emphasizing careful rating in the presence of a variety of sound samples—encourages habits of attending to auditory detail. Certain preliminary stages of auricular training are thus covered while the hearing aid selection program is in progress.

Step 9.—The three (occasionally four) instruments best suited to the patient's needs are picked out for further testing. Ordinarily the instruments with the highest listening hour scores are chosen. However, if there is unusual discrepancy between the scores and the patient's preference, the latter may be the basis for selecting one of the three instruments.

Step 10.—The "hearing aid evaluation" is a final test for the purpose of selecting the instrument to be issued permanently to the patient. Here controlled measures are made on instruments which survive the preceding steps. The series of measures includes determination of each instrument's efficiency (1) in reducing the loss for speech reception, (2) in transmitting loud sounds without undue discomfort, (3) in transmitting speech against a background noise and (4) in allowing speech discrimination. In these measures the patient and the instrument are considered as interacting to produce a functioning unit. All tests are conducted while the patient wears the instrument.

The hearing aid evaluation test is conducted in a soundproof and highly sound-treated chamber. The chamber is empty except for a high fidelity loud-speaker in one corner, a small chair for the subject and an acoustic tile baffle (1 foot [30 cm.] square) above the chair. The hearing aids to be tested are mounted one at a time—flush with and at the center of the baffle. Figure 2 illustrates the arrangement. All test material is presented to the patient through the loud-speaker.

The tester occupies an adjacent sound-treated booth, in which the controls for the test equipment are located. The equipment contains three electrical channels. The first is the live voice channel, which carries material spoken by the tester. This channel consists of a micro-

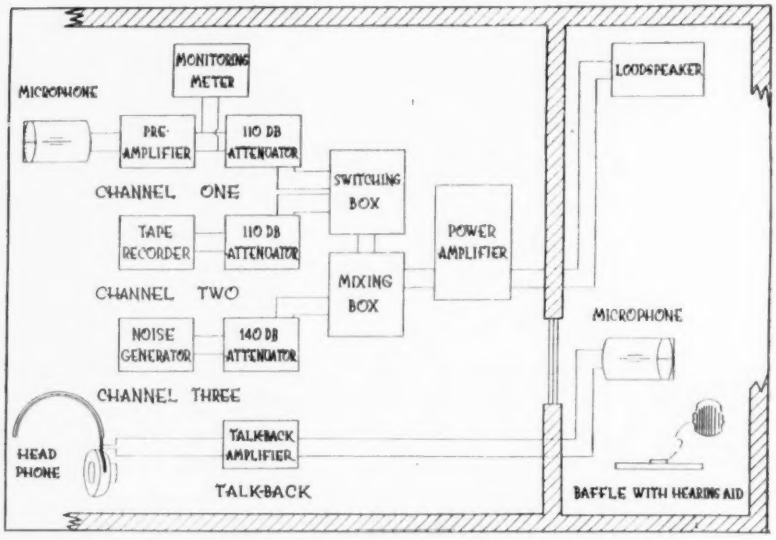

Fig. 2.—Assembly used in hearing aid evaluation tests.

phone, a preamplifier, a monitoring meter and a 110 decibel attenuator. The second channel carries constant level speech. Here a tape recorder plays continuously a recording of simple descriptive material. The tape recorder also feeds into a 110 decibel attenuator. The third channel is for the presentation of noise. Here a generator capable of producing irregular yet relatively stable noise feeds into a 140 decibel attenuator. All channels are connected to a power amplifier, which drives the loud-speaker in the room with the patient. A switching arrangement allows the tester to select either the first or the second channel. The level in either may be controlled at will. The noise may then be mixed with either or may be removed by attenuation. Incidentally, a talk-back system allows the tester to hear the patient. Under ordinary circumstances the patient's ability to hear the test material is determined by

having him repeat it. The tester listens to the patient's responses and makes appropriate adjustments in the equipment as the various measures are determined.

The details of the test itself may now be described. After preliminary instructions, the patient stands facing the loud-speaker with his head against the baffle. His binaural threshold of speech reception without an aid is determined. Here, as subsequently, equated word tests are used unless special difficulties demand sentences. The loss for speech thus obtained gives a check against the speech reception thresholds obtained during the earlier audiometric studies and a base for determining improvement in sensitivity with each hearing aid. At this stage the patient also takes a word discrimination test presented at a level 25 decibels above his unaided binaural threshold. This test serves as a foundation from which each instrument may be judged as to discriminative efficiency.

The first hearing aid is then placed on the baffle and is adjusted by the patient to his "40 decibel comfort level." To clarify, this is a method for setting the volume control at a definite level so that the measures made with one hearing aid may be compared with those made with another. The rationale of the method is simple. In the typical everyday situation the patient will particularly wish to hear a certain person or a specific set of sound signals. He will therefore set the volume control on the instrument so that it brings in optimally this material—so that the reception of the material is most "comfortable." The relative efficiencies of two different instruments in this situation will depend partly on the clarity with which the main signal is transmitted and partly on the range of other sounds which each instrument will handle. To compare them as to their efficiency in this situation it is merely necessary to have the patient set each instrument so that the main signal is coming in most comfortably. The two hearing aids are then equated on functional grounds. They are equated in terms of the way the patient will use them. Their volume control settings may be considered psychophysically equal—and the electroacoustic equivalence of the two settings may be disregarded.

The foregoing rationale is easily applied to the hearing aid evaluation procedures. Speech at a predetermined level is fed into the testing room, and the patient sets his instrument to receive this speech "most comfortably." If the speech is presented at 40 decibels above the normal threshold, the patient's setting is said to be at the "40 decibel comfort level." If 50 decibel speech is presented, the setting is at the "50 decibel comfort level." In practice the tester uses the constant level signal from channel 2. When this signal is appropriately attenuated, the patient sets the aid so that the material is "comfortable."

Statistical analysis reveals that, on the average, when the patient uses the comfort level method to make repeated settings with the same hearing aid, his threshold with the second setting will not be more than 4 decibels from that of the first. This is relatively high reliability. Differences of 8 to 10 decibels between two hearing aids may therefore be interpreted as representing real variations in performance. In practice the hearing aid evaluation test is arranged so that the reliability of each patient may be estimated from the test results. Extra allowances are then made in interpreting these results whenever the patient proves to be inaccurate in his volume control settings.

Once the patient has set the first instrument under test at the 40 decibel comfort level, the threshold of the aided speech reception is determined. The difference between it and the threshold of the unaided speech reception is the measure of the improvement which the instrument gives. Incidentally, the reason for using the 40 decibel level is that this level represents speech which is fairly faint and yet is rather common in everyday life. It is a practical yet exacting level.

With the instrument still set at the 40 decibel comfort level, the limit of tolerance is determined. To do so, the constant level speech is presented at increasing intensities until definite discomfort is reached or until the patient can tolerate the signal when it is 85 decibels above normal threshold. If the patient has no difficulty when the 85 decibel signal is striking the hearing aid, it may be assumed that the instrument is satisfactory from the standpoint of tolerance. From the foregoing measures, the efficiency range of the instrument is computed. This is the difference between the threshold and the tolerance limit.

Next, the hearing aid is turned to full volume. The measures of sensitivity and tolerance are repeated, and the efficiency range at full volume figured. The maximal performance of the hearing aid is thus found.

Third, the setting of the hearing aid is adjusted to bring in 50 decibel speech most comfortably. The tester then measures reception in the presence of background noise. Equated words (or, if necessary, questions) are presented by live voice through channel 1. The material reaches the patient at a level of 50 decibels above normal threshold. Noise from channel 2 is mixed with live voice material. The noise level is varied systematically to determine the maximum intensity in the presence of which the speech can still be repeated. The ratio (in decibels) of this noise level to that of the speech indicates the limit of efficiency of the instrument in background noise.

The hearing aid is again adjusted to the 40 decibel comfort level. As a recheck, the threshold of the aided speech reception is measured a second time. Without changing the volume control, a word discrimination test, or articulation test, is then administered by live voice at a

level 25 decibels above the threshold just determined. This indicates the discriminative efficiency of the instrument.

At the discretion of the tester, other measures are also repeated. The patient is then ready to test the next hearing aid in the same way.

The foregoing procedures, of course, have to be modified for special cases. Three primary problems appear. First, patients with severe loss may not get efficient results at the 40 or 50 decibel comfort settings. In these cases, a higher signal level is used for adjustment to the most comfortable loudness, the main requisite being to employ the same setting on all instruments tested. Second, some patients find the test too difficult for their linguistic or perceptual abilities. Sentences are often usable when equated word lists are not, but the tester must sometimes use great ingenuity in adapting to a patient's special needs. Finally, a few patients have severe difficulties of tolerance or other special problems which demand appropriate modification of procedures.

Step 11.—The results of the hearing aid evaluation test plus the audiometric and listening hour results are reviewed by the person in charge of the Acoustic Clinic. This person confers with the patient and specifies which instrument is to be issued. The selection of the final hearing aid calls for a weighing of many factors. Strong emphasis is given to sensitivity, limits of tolerance, performance in noise and discriminative efficiency. However, it is seldom that one instrument outperforms all others on every count. At times an instrument superior on one point is inferior on another. In the majority of cases, nevertheless, definite superiority emerges on at least one measure. Obviously, the final choice must take into account both the relations between hearing aids and the degrees to which the aids yield results that approximate normal hearing. The task is to estimate from the test results the difficulties and the benefits which the patient will experience in everyday situations.

For example, the limits of tolerance may be the prime basis for decision (with complete disregard of sensitivity) provided all instruments yield residual losses of 10 decibels or less. When the residual losses are at the 30 to 40 decibel level, however, differences in sensitivity may outweigh either tolerance or performance in noise. Under ordinary circumstances, of course, particular emphasis is given to discrimination scores. Where significant differences in these emerge, there must be exceptionally strong advantages on other points before the instrument with the poorer score on the articulation test is picked.

Two or more instruments may show approximately equivalent performance. When this is the case, choice is based on relative performance in the listening hour, on patient preference and on special considerations of service and general practicability. The patient is questioned carefully before this type of selection is made—and the basic policy is

carefully followed: namely, the facts at hand are judged with the goal of estimating which instrument promises greatest efficiency and satisfaction in everyday performance.

As soon as the final selection is made, the instrument chosen is issued to the patient, along with necessary batteries and other accessories. The patient keeps this instrument permanently.

Step 12.—Attention to a patient's hearing aid does not cease when he has received his own instrument.

Each patient is given careful instruction in the care and the maintenance of his hearing aid.

Each patient receives formal auricular training with his own aid. This training is as extensive as his needs demand.

Finally, the use of the aid is incorporated in the patient's speech correction and lip-reading work in whatever manner his instructors deem wisest.

These matters, however, lie beyond the scope of a paper on selection of hearing aids. They, therefore, need not be discussed further. Suffice it to say that the goal in all phases of the Aural Rehabilitation Program is to encourage and teach each man to use his hearing aid with the maximum efficiency. The goal is to bring each man to as high a performance level in human communication as his deficiencies will allow.

V

In summary, the Deshon program for the selection of hearing aids consists of four major parts:

1. Initial exploration of each patient's needs and appropriate decisions based on these needs;

2. Preliminary screening to eliminate undesirable instruments and reduce to a workable number the instruments which are sufficiently promising to warrant further study;

3. Further screening through the "trial use period" and through the "listening hour" to select the three most promising instruments;

4. Detailed testing—in the "hearing aid evaluation"—to determine which of the three instruments yields superior performance when worn by the patient.

OFFICE STUDY OF CILIA

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SOME years ago, after reading one of Proetz's papers describing his observations on respiratory cilia, I mentioned to Robert J. Hunter my envy of any one who had a laboratory in which so fascinating a subject could be investigated. Dr. Hunter retorted, "All you need in order to study cilia is a patient and some lamp black!" Procuring both, I began to study.

It was observed that there were wide variations in the ability of different noses to cleanse themselves (via cilia) and that there could be just as great variations in the same nose at different times. Too often, however, I was unable to make the repeated observations I desired on the same patient, because of his objections to the messy lamp black. It was not feasible properly to indoctrinate the patient with the desired degree of scientific enthusiasm; he seemed to consider laundering difficulties of paramount importance. An added handicap was the difficulty of observing the dark material in the posterior recesses of the nose and in the infraturbinal meatuses through the nasopharyngoscope, or by posterior rhinoscopy. Attempts to photograph its progress were futile. It was not recognizable at all on black and white film and scarcely on color film.

During this period I had made a hobby of trying to guess, from inspection of the nasal mucosa, how recently feminine patients had powdered their noses. All rhinologists have noticed the frequency with which the mucosal surfaces will be covered with face powder because the patient has sniffed while using her powder puff. That powder, held by the sticky mucus, will be moved as ciliary action transports the mucus; in that respect it differs from lamp black only in being more easily visible. While I was pondering the suitability of face powder as a general medium, the Micraform crystals of sulfathiazole were introduced. They have been very satisfactory for this study.

The microcrystals may be used dry in a powder blower or as a 5 per cent suspension in an atomizer such as the no. 152 DeVilbiss. In most cases I use the latter. One may spray the mucosa with a suspension of paredrine hydrobromide and sulfathiazole [1] and then make observa-

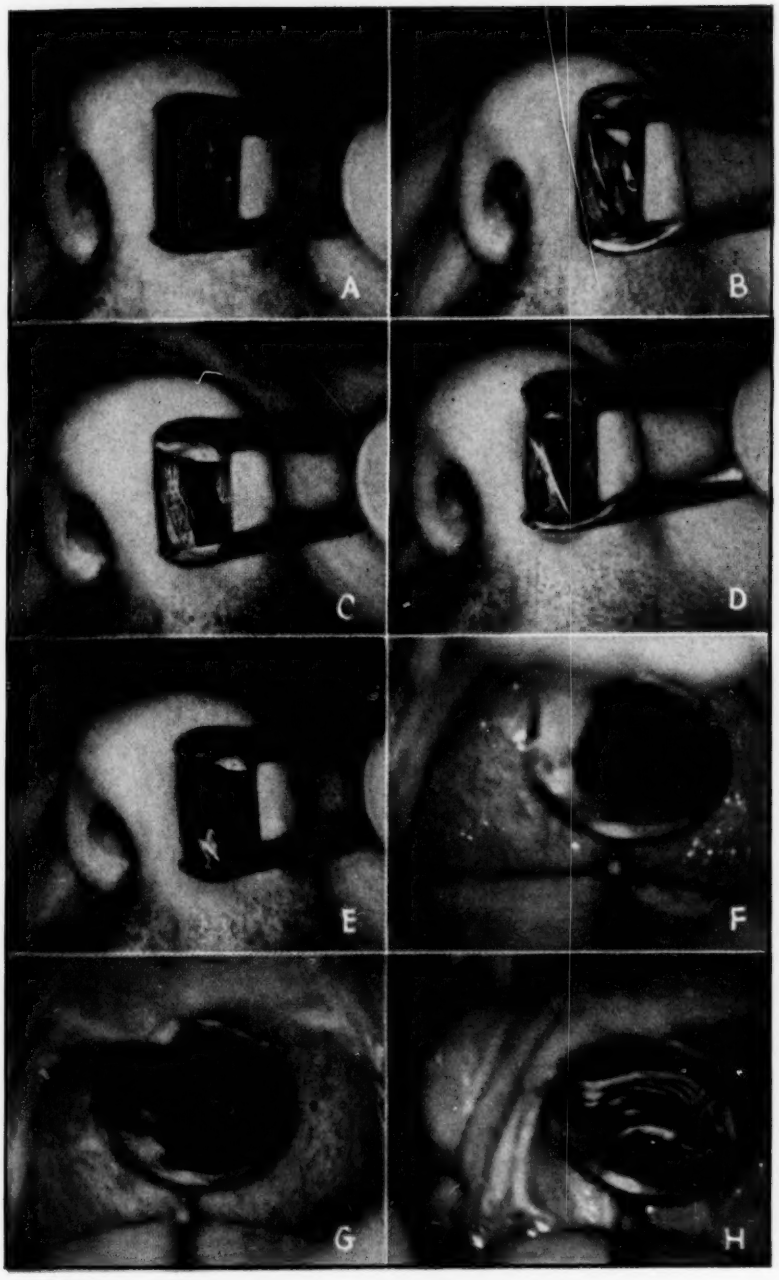
1. Paredrine hydrobromide is parahydroxy-α-methylphenylethylamine hydrobromide. The suspension contains 5 per cent microcrystalline sulfathiazole in 1 per cent aqueous solution of paredrine hydrobromide.

tions at intervals of a minute or two, but in fairly healthy noses most of the crystals will have disappeared by the time complete shrinkage has taken place. When careful inspection is desirable I prefer to shrink the membranes first. I use 1 part of 2 per cent tetracaine hydrochloride to 3 parts of 1 per cent neo-synephrine hydrochloride in a hard rubber atomizer (no. 286) or on cotton-tipped applicators applied to the areas of the anterior and the posterior ethmoidal artery as though for submucous resection. This gives not only swift shrinkage but enough anesthesia to permit careful inspection of all parts of the intranasal concourse with the nasopharyngoscope. However, the rhinologist may use whatever aqueous solution he prefers as a shrinking agent, because I have found none of those which I have tested to have a deleterious action on the cilia after a single application.

After the common meatus has been opened to inspection, a quick burst of sulfathiazole crystals, with the nozzle directed toward the septum and traversing an arc from the bridge to the floor of the nose, will be found to have covered most of the visible surface with a frosting of white. Any area not reached may be sprayed again. The ensuing streaming may be followed readily with the eye or recorded on film. There is no esthetic objection to the use of sulfathiazole crystals on the part of the patient, but he should be asked about the possibility of allergy to them. I have found such a condition to be extremely infrequent.

Although the intranasal ciliary pathways have been adequately described by Proetz and others, no rhinologist can fail to thrill at the opportunity to observe for himself the divers patterns in different noses. The clearing of infection in any nose will be accompanied by a return of ciliary action in part at least; failure to return completely to normal suggests continued infection or structural abnormality which impairs the normal air currents in the nose.

In a normal nose, as one watches, the crystals will be seen to coalesce rapidly into small flecks. These are gathered together to form streams which merge to flow purposefully toward the nasopharynx. Secretions from the septum will be seen to reach mainly the floor of the common meatus over the soft palate. In the vestibule and on the anterior convexities of the middle and inferior turbinates the inrushing current of air tends to dry the mucosa, so that the crystals remain unmoved in those areas until washed away by excess of mucus from elsewhere. In sharp contrast, the crystals are moved swiftly from the medial surfaces of the turbinates and are carried backward and downward to disappear under the free margins. In wide noses they may be followed farther with the nasopharyngoscope. In most noses they can be seen by posterior mirror examination as they appear from beneath the turbinates. In the nasopharynx their course is inconstant. They may flow down the posterior pharyngeal wall as a small stream on each side, showing



A, 8:12. Septum has been sprayed with microcrystals of sulfathiazole. *B*, 8:16. The crystals recede. Note the serrated margin near the nasal bridge. *C*, 8:24. The septum is clean except in the area of the vestibule. *D*, 8:31. Posteriorly the cilia pull on the mucus sheet in the vestibule and break it. *E*, 8:35. The vestibule is clean; the patient is only convalescent; twenty-three minutes is too long for this chain of events. In *F* a stream of pus from the right ethmoid cells crosses the nasopharynx and the left torus tubarius. In *G* the crystals follow the same course, showing the ciliary pattern. In *H* the crystals move posteriorly in waves after being instilled as drops; the head in Proetz's position.

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how infectious matter can cause hyperplasia of the lateral pharyngeal bands. They may spread out and come down diffusely over the posterior wall, whitewashing it. They may split, part running behind the torus tubarius and part joining the puddle on the floor of the nose. The stream may run directly over the torus itself! (See *F* in the figure.) It may run across to the opposite side of the nasopharynx and then follow any of the routes already described. The only apparent cause I have found for this variability is the vast array of variegated scar patterns and lymphoid remnants in the adenoid area. When more data are available, this will be made the subject of another paper. The sundry scars from too forceful and widespread adenoidectomies I have observed to be a potent cause of some of the complaints referred to the rhinopharynx—largely because of their interference with normal ciliary currents. Inspection of a series of throats will reveal webs, pockets and adhesions of the most bizarre and irregular arrangement, around which normal streaming takes place but on which there is found no evidence of ciliary action. The result is that matter which lodges on or within these areas accumulates and may cause discomfort and sometimes odor until at last it falls into the pharynx by reason of its own weight. One sees the same result where the air current is unimpeded and strikes the posterior pharyngeal wall with force. This may be because of septal deflection giving too large a common meatus on one side, to removal of the middle turbinate, to atrophic rhinitis or to too frequent use of powerful intranasal vasoconstrictors. Whatever the cause the result may be observed readily if one will take the time to make repeated observations with a postnasal mirror or with the antroscope. The dry area, if it has been covered with the crystals, remains unchanged and looks as though whitewashed. Around it the white flecks merge to form streams which become confluent to pursue their normal paths.

All this is beautiful to watch and, like any of Nature's marvels, must be seen to be appreciated. But, says the busy rhinologist, what of it?

The normal must be observed, and repeatedly, before the abnormal can be appreciated and the extent of its deviation appraised. The more often one watches the action of these crystals on mucous membranes, the more one can learn from it. In some doubtful cases their action is diagnostic. I shall mention a few examples.

Septal aberrations are common, but only a picture straightener will want to correct all of them. If one is in doubt as to whether a deviation is provoking symptoms, both sides of the septum may be sprayed with the crystals. Then it may be found that the crystals have dried on a jutting spur, pocketed in an eddy behind it, and move sluggishly if at all on the concave side, where cilia have degenerated because of the slow interchange of air. Therefore, one may feel confident that a

complete submucous resection will aid in the restoration of normal nasal function.

While I have been unable to correlate the color of the nasal mucous membrane with the degree of severity or the extent of intranasal infection, the ciliary activity is found to be a fairly accurate index. For example, inspection may show the pale lavender mucosa of allergy on the turbinates. Allergy does not impair ciliary activity. If there is impairment, displacement probably will produce a quantity of yellow pus, notwithstanding the apparent lack of inflammation of the membranes. Of course, it is to be remembered that pus may be obtained even in the presence of good ciliary action. In the absence of the normal ability of the nose to cleanse itself, infection is certain even if pus is not seen. There is the thick and red mucosa which may be secondary to pelvic congestion, prostatitis, sexual excess or overuse of strong vasoconstrictors. If there is no infection locally, the crystals will disappear rapidly from such a surface. If they do not, there is infection even though no pus is to be seen; the infection may be intramucosal. In this type of case the disease is especially likely to respond to autogenous vaccines and mild local therapy.

If the patient has been using a sulfathiazole suspension as nasal drops, it will be found interesting to attempt to estimate, on inspection of the nose, how long an interval has passed since the last previous application. If that was at bedtime and the crystals are still to be seen after routine shrinkage in the office in the morning, impairment is manifest. Search should be made in the infraturbinal meatuses, the sphenoethmoidal recesses and the nasopharynx. If the search is successful, it is more diagnostic than roentgen examination which, even though it show clouding, cannot differentiate between allergic and inflammatory edema.

With the nasopharyngoscope in place, the eustachian orifices may be observed while the patient swallows. If there is a puddle of pus or mucus mixed with sulfathiazole on the floor of the nose, where it usually collects, it may be seen to be squeezed against the torus as the constrictors contract. Of course, the auditory tube opens at the same time. Does it not seem that this is a more plausible explanation of aural infection, especially that in infants, than "hyperplastic adenoids?" Rarely does one see adenoids bulging into the posterior choanae and actually occluding the torus. Rarely does one see impaired ciliary activity on the adenoids. My observations lead me to believe that if adenoids are infected they may have become so secondarily to suppurative ethmoiditis, the "most frequently missed diagnosis in medicine." The same mechanism is at work with the tonsils. During the act of deglutition some of the sulfathiazole crystals may be brought forward and left in the tonsil crypts. This happens so commonly that one cannot help wondering whether it is not possible that the tonsils become overwhelmed by

infection from the ethmoid sinuses rather than vice versa. One rarely removes tonsils now except when there is a history of definite tonsillitis, recurrent. Time taken properly to observe and, if necessary, to treat the ethmoid cells is productive of a more beneficial result.

My conclusions, as stated, are inferences only. I realize that they sound radical as compared with teachings in the past. I request only that before they are condemned, the doubter take the trouble to test this method for himself and to observe, painstakingly, by every route, as much as he can see of the inside of the nose and the nasopharynx. He can be assured of an enjoyable study.

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NONEXPERIMENTAL PATHOLOGIC NASAL FINDINGS IN LABORATORY RATS

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INVESTIGATIONS of the effects of drugs on the mucous membranes of the nose have been encouraged by the fact that in various laboratory animals the nasal mucous membranes are easily accessible for such study and the effects of the drugs can be observed without the function of other vital organs being interfered with.

The basis for this type of experiment is complete orientation as to (1) the normal anatomy and histology of the animal in question and (2) knowledge of pathologic conditions as they are encountered spontaneously, i.e., in the course of the normal life under laboratory conditions or in the animal farms of the institutions without exposure to experimental factors. Rabbits are generally preferred in such work, but dogs, cats, mice, rats, ferrets and monkeys are frequently used.

Two groups of drugs are examined by this assay: (1) medicaments used locally in the treatment of nasal conditions and (2) agents administered parenterally by the intranasal route to produce systemic effects. With the increase in the number of drugs available for intranasal use there is a corresponding extension of investigations of the use of drops, sprays, powders and jellies, irrigations from the nose or from the choanae, packings, smoke inhalations, iontophoretic applications, and injections of the nasal tissues. However, in the case of either type of drug the evaluation of the local effect can best be made by comparison with the untreated area or with the litter mate which has been untreated or treated with some neutral solution such as isotonic solution of sodium chloride.

It has been felt that the progress of such experimental work needs more data as to the normal conditions and the "spontaneous" pathologic phenomena. In 1941 Hilding [1] remarked that it would be helpful to

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This investigation was aided by grants of the Charlton Fund, Tufts College Medical School, and of Wallace and Tiernan Products, Inc.

1. Hilding, A. C.: Experimental Sinus Surgery: Effects of Operative Windows on Normal Sinuses, Ann. Otol., Rhin. & Laryng. **50**:379-392 (June) 1941.

know the incidence of spontaneous sinusitis in rabbits. In the course of his investigations he repeatedly noted infected sinuses in otherwise apparently healthy animals; he found that when a rabbit becomes ill or debilitated, rhinitis and sinusitis are prone to develop.

For such reasons, it seems desirable that a well defined picture be obtained in regard to the anatomy, the histologic appearance and the nonexperimental pathologic conditions encountered intranasally in each kind of laboratory animal that is generally used. The present study has been made of the rat as one type of laboratory animal readily available and frequently used in experimentation with drugs.

MATERIAL AND METHODS

In order to obtain data from a cross section of the species rather than from a single strain of a single laboratory, 40 animals of both sexes and of different but known strains of various laboratories were used. They had been employed solely for breeding purposes, and their diet had been a normal one designed to maintain a high standard of general good health. Their weight varied between 82 and 285 Gm., with an average of 212.1 Gm.

Since the comparison of results would be more difficult if we sought to reproduce different procedures used by others, the following simple technic was adapted: The rats were decapitated, and the heads were preserved from one to four weeks in a 4 per cent solution of formaldehyde. At the end of this time, the lower jaw was cut off, and the skin and the muscles were removed. No skeletal parts were touched to avoid fractures, which continue easily into the delicate framework of the structures of the nasal cavity. Decalcification was carried out by nitric, trichloroacetic or formic acid. After a degree of softness had been obtained which permitted cutting through the bones of the skull with a razor blade, a tissue block containing the nasal cavity was carved and submitted to further short decalcification. After paraffin embedding, a series of frontal sections were cut through the entire length of the nasal cavity. An average of forty sections per animal, stained with hematoxylin-eosin, were examined. In this way a complete survey was possible, including the nasal walls, the turbinal apparatus and the spaces between them, and the sinuses, the latter said to be variable not only as to location but even as to their presence.[2]

GENERAL CONSIDERATIONS

Before reporting the findings in detail, we should consider shortly the anatomy and the histology of the nose of the rat. While the histology, especially that of the olfactory region and of Jacobson's organ,

2. The histologic work was carried out by Miss Alva Dellamano, Miss Dorothy Linden and Miss Anna Morse. The drawings were executed by Miss Muriel P. McLatchie, director of the School of Medical Illustration of the Massachusetts General Hospital, and the photomicrographs were prepared by Richard W. St. Clair, head of the Photographic Laboratory of the Massachusetts General Hospital.

has been discussed in full detail by Kolmer,[3] and the comparative anatomy of the central olfactory system by Brunner,[4] the macroscopic anatomy and the disposition and the structure of the turbinates and the paranasal sinuses have to be compiled from numerous sources which are widely different in their interests and often contradictory. Monographs on the anatomy of the rat are sketchy in regard to the nose, and illustrations of the nasal cavity are few; textbooks on comparative anatomy mention the conditions found in the nasal cavity of the rat only in the barest outline. Accordingly, a correlated picture of the main findings of many authors may be of some value (figs. 1 to 4*B*).

Anatomy.—From the standpoint of the intranasal application of drugs the main difference between the nasal cavity of man and that of the rat is in the disposition of the ethmoid region. The ethmoid sinus of man is a closed system of cells with narrow openings; the lumens of the cells can be reached by drugs only by special measures such as the displacement method described by Proetz.[5] In the rat, as in numerous other mammals, the ethmoid region is just the enlarged posterosuperior part of the nasal cavity, containing turbinates instead of the cells of the human anatomy. Except for their comparative remoteness, the space between them, or the space between the turbinates and the septum, can be reached as easily as any part of the human nasal cavity.

As in all the macrosmatic mammals, the posterosuperior olfactory region of the nose is highly developed in the rat, whereas the respiratory region represents merely a comparatively simple pathway leading from the nostrils to the pharynx. The turbinal apparatus corresponds to the general disposition in mammals in a comparatively simple form. Since the nasal cavity is long and low, the ethmoid part is located behind the respiratory region.

Two systems of turbinals are well defined. The nasoturbinal, corresponding to the human agger nasi, forms a long and slightly curved ridge directly underneath the nasal bone; the maxilloturbinal originates from the lateral wall in the anterior part of the nasal cavity. Both are generally simple coils and are covered with purely respiratory epithelium. Opposite the anterior part of the maxilloturbinal on the septum is located Jacobson's vomeronasal organ. The maximal development of this organ is seen in rats; however, in the evaluation of pharmacologic experiments this is of minor importance, since in man the corresponding elements are rudimentary and only in rare instances does any noteworthy pathologic change occur (Kelemen[6]).

Far more complicated is the ethmoid region where the second group of projections, the ethmoturbinals, are located. They are covered almost entirely

3. Kolmer, W.: Normale Anatomie der Nase, in Jaffé, R.: Anatomie und Pathologie der Spontanerkrankungen der kleinen Laboratoriumstiere, Berlin, Julius Springer, 1931, pp. 11-24.

4. Brunner, H.: Entwicklung des Geruchsorganes und Physiologie des zentralen Riechapparates beim Menschen und beim makrosmatischen Tiere, in Denker, A., and Kahler, O.: Handbuch der Hals- Nasen- und Ohrenheilkunde, Berlin, Julius Springer, 1925, vol. 1, pp. 174-176.

5. Proetz, A. W.: The Displacement Method of Sinus Diagnosis and Treatment, ed. 2, St. Louis, Annals Publishing Company, 1939.

6. Kelemen, G.: Occlusione anteriore bilaterale del naso per anomalia di formazione: Cisti dell' organo di Jacobson? Rassegna ital. di otol. **7**:137-141, 1933.

Fig. 1.—Sagittal sections showing the lateral nasal wall after removal of the nasal septum. For explanation see figure 2.

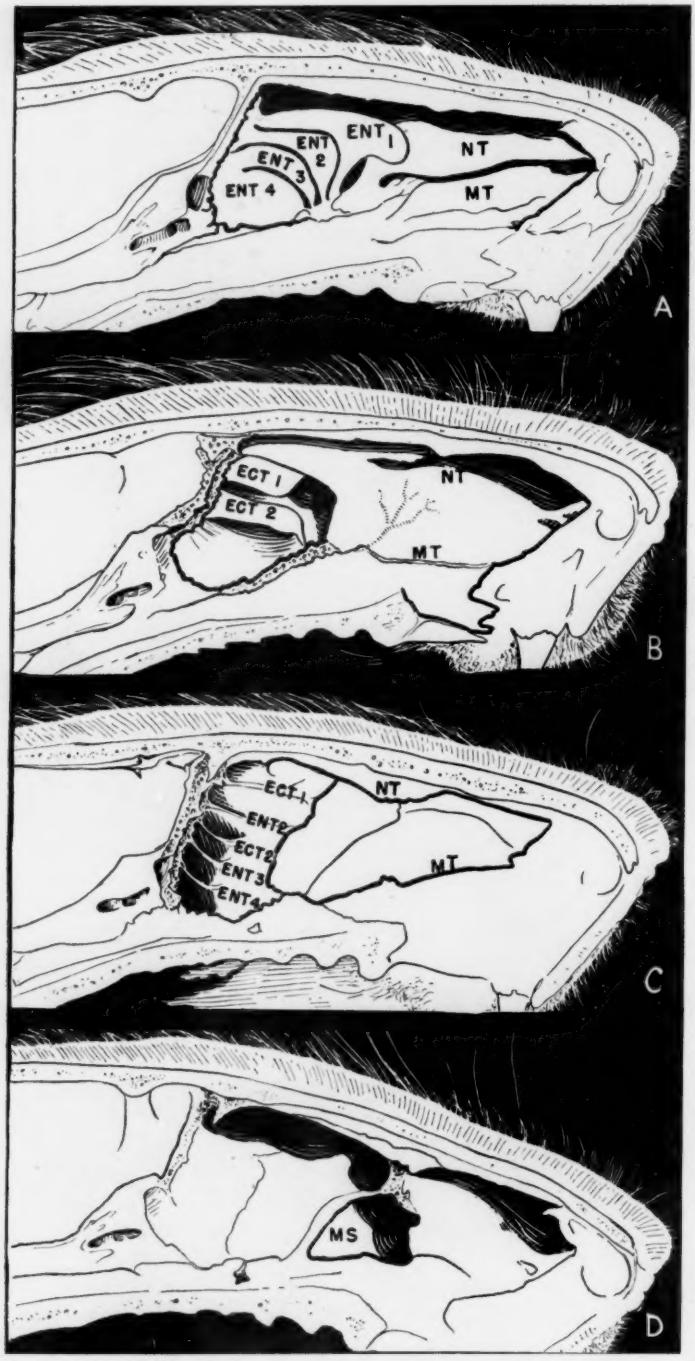

Fig. 2.—*A*, lateral nasal wall after removal of the septum: *NT*, nasoturbinal; *MT*, maxilloturbinal; *ENT*, endoturbinal.

B, lateral nasal wall after removal of *NT*, *MT* and *ENT 1* to *4*. *ECT*, ectoturbinal.

C, lateral nasal wall after removal of all turbinals.

D, same as *C* with medial wall of maxillary sinus removed: *MS*, maxillary sinus.

by olfactory epithelium and are disposed in two rows, termed endoturbinals and ectoturbinals. A structure of the latter type is observed as a supernumerary ridge in the human embryo. The former are simple or double scrolls; after removal of the septum their free edges resemble longitudinal cushions running in a direction from posterior-superior to anterior-inferior with a slight curve, directed with their convexity upward. The ectoturbinals are similar but may be seen only after removal of the endoturbinals; they are situated underneath and behind the folds of the endoturbinals (hence, their alternate name, concha obtecta). Both groups represent true independent turbinals, as each arises separately from the wall of the ethmoid bone with an individual stem. However, two of them may present a common root. The rat has four endoturbinals and five olfactory folds. The basal lamella of the second endoturbinal is divided into two parts shortly after its origin, and each forms its own scroll. They cover two ectoturbinals, the first located between the first and second, the second between the second and third endoturbinal. Each turbinal with its free projection represents an olfactory lobe; the rat has seven on each side, five belonging to the endoturbinals and two to the ectoturbinals. The number of ectoturbinals is small in comparison with the number in other mammals. The maximum, thirty-one, is seen in the horse.

The data in the literature as to the maxillary and frontal sinuses of the rat are widely divergent. The large posterosuperior olfactory space penetrates deeply into the body of the presphenoid, and a true sphenoid sinus does not exist. In this way the body of the sphenoid bone serves to enlarge the upper part of the nasal cavity. Paulli [7] described in Mus decumanus a high, narrow, short cavity inside the maxilla, with a short prolongation into the marsupium; in Mus musculus the cavity is much reduced in size; the maxillary sinus may be prolonged into the body of the nasoturbinal and even into the nasal bones. Another sinus, corresponding to the frontal, may also be seen as an enlargement of the main nasal cavity and may contain parts of the ethmoturbinalia (Gegenbaur [8]). Cuvier [9] could not find sphenoid or maxillary sinuses in rodentia; Wiedemann [10] found no frontal sinuses. According to Zuckerkandl,[11] both the sphenoid and the frontal sinus are represented by shallow depressions of the main nasal cavity containing parts of the olfactory lobes (free projecting ends of the olfactory plates); the maxillary sinus is very narrow because the alveolus of the canine teeth [12] takes up much space. Fenton and Larsell [13] found that while the lining of the turbinals and of the septum is highly vascularized and well exposed, that of the

7. Paulli, S.: Ueber die Pneumaticitaet des Schaedels bei den Saeugetieren, Morphol. Jahrb. **28**:147-178 (Dec.) 1899; 179-251 (June) 1900; 483-564 (Sept.) 1900.

8. Gegenbaur, C.: Vom Riechorgan, in Vergleichende Anatomie der Wirbelthiere, Leipzig, W. Engelmann, 1898, pp. 950-971.

9. Cuvier, G., cited by Zuckerkandl.[11]

10. Wiedemann, C. R. W., cited by Zuckerkandl.[11]

11. Zuckerkandl, E.: Das periphere Geruchsorgan der Saeugetiere, Stuttgart, F. Enke, 1887.

12. Molar teeth have to be substituted here as the dental formula of rats does not contain canine teeth.

13. Fenton, R. A., and Larsell, O.: Some Experimental and Clinical Observations on the "Reticulo-Endothelial" Components of Accessory Sinus Mucosa, Tr. Am. Acad. Ophth. **36**:225-238 (Sept.) 1931.

accessory sinuses (cat) is poorly aerated and vestigial. Dietz [14] found a normal nasal p_H of 7.2 at 35 C. in rats.

In addition to this anatomic outline as a basis for discussion of experimental findings, two other factors should be considered. First, the spontaneous changes found under laboratory conditions, and, second, the findings reported after experimental administration of drugs, as recorded in the literature.

Nonexperimental Changes.—Berberich and Nussbaum [15] reported on the spontaneous diseases found in small laboratory animals in their discussion of acute, chronic and specific inflammations, as well as parasitic diseases and neoplasms of the nasal and paranasal sinuses, from the pathologic standpoint. Francis and Stuart-Harris [16a] noted that the air passages of the nasal cavity may occasionally contain a little mucus or cell debris with leukocytes. Ratcliffe [16b] observed inflammatory and suppurative diseases of the lungs as probably the most common of all morbid conditions of adult rats. These conditions are closely related to changes in the nasal cavity as in the case of infection of the middle and inner ear. (The latter is quite common and has been extensively reported in the literature.) Hunnicutt [17] found that even control mice had a little excess mucus on the epithelial surface, which may have been within normal limits. Nelson [18] mentioned that rhinitis with exudate in the nasal passages and hemorrhagic crusting around the nares, frequently in connection with otitis media, occurred in a high percentage in some of his rat colonies; Actinobacillus muris was isolated.

Kolmer [3] observed in rats "not infrequently" catarrhal infiltrations, strictly localized to one side of the nose; sometimes one of the two vomeronasal organs showed pathologic signs. The findings were mostly round cell infiltrations of the epithelium and desquamation. These conditions are particularly significant in considering such experiments as those of Butler and Ivy.[19] Their control study was done by applying the drug to only one nasal chamber; the other side was considered as an ideal blank control for environmental conditions, extraneous infections and possible variations in histologic technic. Rabbits were used in these studies, and unilateral infection of the upper respiratory tract was rare. In their studies of nasal mucosa from normal animals, they noted a great degree of similarity between the specimens from the two nasal chambers.

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14. Dietz, A. A.: p_H of Nasal Mucosa of Some Laboratory Animals, Proc. Soc. Exper. Biol. & Med. **57**:339-341 (Dec.) 1944.

15. Berberich, J., and Nussbaum, R.: Pathologische Anatomie der Nase, in Jaffé, R.: Anatomie und Pathologie der Spontanerkrankungen der kleinen Laboratoriumstiere, Berlin, Julius Springer, 1931, pp. 25-29.

16. (*a*) Francis, T., and Stuart-Harris, C. H.: Studies on the Nasal Histology of Epidemic Influenza Virus in the Ferret, J. Exper. Med. **68**:789-830 (Dec.) 1938. (*b*) Ratcliffe, H. L.: Spontaneous Diseases of Laboratory Rats, in Griffith, J. O., and Farris, E. J.: The Rat in Laboratory Investigation, Philadelphia, J. B. Lippincott Company, 1942.

17. Hunnicutt, L. G.: Reaction of Mucous Membranes to Five Per Cent Solution of Sodium Sulfathiazole, Arch. Otolaryng. **36**:837-842 (Dec.) 1942.

18. Nelson, J. B.: Infectious Catarrh of the Albino Rat, J. Exper. Med. **72**: 645-654, (Dec.) 1940.

19. Butler, D. B., and Ivy, A. C.: Method of Application of Drugs to the Nasal Mucosa, Arch. Otolaryng. **39**:109-123 (Feb.) 1944.

Such spontaneous manifestations should be compared with the changes produced by experimental application of drugs. The following survey is compiled from the reports of many authors concerning damage done to the nasal structures in their experiments. Manifold as they are, these artificial changes can be grouped along some common lines.

Changes Produced by Application of Drugs.—(*a*) Epithelium: A tall, well ciliated form free from cellular infiltration is generally considered as a starting point. The degree of activity is indicated by the number of mitotic figures present. The cell outlines are distinct, the nuclei are normal, the cytoplasm is clear and the goblet cells are scarce. The artificially produced changes can be divided into two groups: hyperplastic and destructive.

With hyperplastic changes, the turbinates appear injected and glistening. General evidence of infection is given by hyperemia, hemorrhage and edema. Yet at the point of application of drugs the mucosa becomes pale. Slight loosening is followed by increasing thickness and pseudostratification. The basal nuclear layer may measure four to five cells in thickness, with indistinct cell walls. Several factors are influential in increasing the subepithelial layer, such as: increase in the size and the number of glands; congestion and dilatation of the vessels; general abundance of cells, best observed in the venous sinuses of the submucosa; general dense cellular infiltration, sometimes with a great number of plasma cells.

Destruction begins with the mucosal lining being reduced to one or two cell layers. This cellular reduction is followed by loss of cell outlines, loss of cilia or clogging of the latter, pyknosis or indistinctness of nuclei and granularity of cytoplasm. Fused nuclei are seen in the basal cells. The destruction may be partial or complete. Complete destruction is characterized by loss of the mucous membrane down to the basal "pavement" layer and to the lamina propria. The membrane may show all phases from occasional areas of ulceration through absence of the epithelium to complete denudation of the underlying cartilage or bone. Stretches of normal epithelium may be surrounded by extensive necrosis. The latter varies from relatively superficial damage to extensive coagulation necrosis with general destruction of the tissues. In this way large areas become denuded. Maximal damage is represented by complete slough. The superficial layers show desquamation partly by flaking off and partly by formation of epithelial blisters. The separation from the lamina propria is effected more or less en masse; ribbons of mucous membrane are found lying free in the meatus, while well stained nuclei in these ribbons confirm the fact that their detachment is recent. Edema of the entire mucosa is more characteristic of the olfactory than of the respiratory system.

(*b*) Cilia: The cilia become indistinct, clump together as if gummed, become entirely lost, or only broken stumps of cilia are seen. The entire ciliary layer becomes spotty, patchy and later indistinguishable.

(*c*) Goblet Cells: These elements, which are cells filled with mucin and without cilia, increase in activity and show a high rate of secretion. Their number increases until they become many more than normal and even absolutely dominant, giving the impression that many cells have become goblet cells.

(*d*) Nonfixed Elements: Marked cellular infiltration is common, the epithelium containing many leukocytes, the majority of them polymorphonuclears, which progress into the mucosal surface and form an exudate. More or less dense infiltration is seen in the submucosa; polymorphonuclear leukocytes, mononuclear

cells, as lymphocytes, plasma cells and macrocytes, and fibroblasts abound. The leukocytes show a tendency to focal arrangement. Pus cells penetrate the epithelium and make it almost unrecognizable.

(*e*) Olfactory Elements: These show many changes, such as edema of the olfactory bundles in the subepithelial layer, degenerative changes in the nerve fibers, cellular infiltration and vacuolation in large fibers, and fatty degeneration with destruction of the axon.

(*f*) Secretions: Mucus is found in small amounts or in droplets on the surface or in slight excess; the mucous blanket over the turbinates may be thickened or clumped, with irregular breaks in continuity. The amount of exudate is moderate, with a few pus cells on the surface of the epithelium or in large thick mucopurulent masses. The exudate is watery or more or less dense and consists of leukocytes, desquamated and necrotic epithelial cells, nuclei and debris.

(*g*) Paranasal Sinuses: The normal epithelial surface is glistening and pale; it becomes thickened by irritation and changes to a dull appearance, with friability (Fenton and Larsell [13]). Knowlton and McGregor [20] found that in dogs the number of goblet cells in the normal mucosa of the maxillary sinus is extremely small but that the number of glands is greater than in the human sinus. Purulent infection with exudate filling the sinuses was observed occasionally with dried secretions in the cavities. Fenton and Larsell [13] produced destructive changes in the frontal mucosa in cats by injecting various chemical agents; remarkable findings were deep cysts with broken-down epithelium. Toward the ostium, acute or chronic edema was seen, the latter with capillary dilatation.

Regeneration.—If the destructive agent applied is not too concentrated or is brought into contact with the tissues for only a short time, regeneration will follow. The exudate in the passages becomes less dense. The regeneration of the epithelium may be complete even to the formation of cilia, although the new covering is often more cellular and at the same time half as thick as normal; on the other hand, the newly formed lining may attain much more than normal thickness. The nuclei of regenerating epithelium are for a while hyperchromatic. After the damaged epithelium separates from the lamina propria, general repair follows rapidly. The beginning of reepithelization is marked by activity in the subepithelial layer. Polyblasts and fibroblasts make their appearance. In fact, Fenton [21] found that, of all the mucous membranes of the respiratory tract, the submucous stroma has by far the greatest reparative power; epithelium with a healthy stroma below it is speedily repaired. Histiocytes are in the first line of defense and repair; they appear ahead of polymorphonuclears and lymphocytes. The number of polyblasts diminishes with increased formation of fibrous tissue. Fibrosis is responsible for a grossly thicker, paler mucosa; a great increase of connective tissue takes place, with heavy fibrous tissue filling out occasional defects in the septum. Fibroblasts replace the mononuclear and polymorphonuclear cells in the interstitial tissue. In the cartilage, multinucleated chondroclasts appear, breaking up the cartilage. Fibroblasts may be converted into chondroblasts. The fibrosis includes even the blood vessels. In the midst of this fibrosis, the subepithelial glands are regenerated.

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20. Knowlton, C. D., and McGregor, G. W.: How and When the Mucous Membrane of the Maxillary Sinus Regenerates, Arch. Otolaryng. **8**:647-656 (Dec.) 1928.

21. Fenton, R. A.: Certain Reactions of Laryngeal Tissues to Medicinal Agents, Arch. Otolaryng. **32**:429-433 (Sept.) 1940.

Regeneration can be completed by replacing the original epithelial type by another; besides transitional forms, several others appear, as in the respiratory tract epithelial types are interchangeable according to the circumstances.

The two main types of epithelium found in the nasal cavity are characterized by important differences of regeneration. In experiments in which only the basement membrane and the basal cells are preserved, flattened cells begin to accumulate in the respiratory area and form a layer or two of thickening epithelium. Francis and Stuart-Harris [16a] reported that in the laminas of the posterior turbinate, which are partly covered by respiratory and partly by olfactory epithelium, an abrupt transition between the necrotic zone of the former and the normal structure of the latter was seen.

Stratification plays an important role; pseudostratified and metaplastic areas appear, or areas of stratified squamous elements, between regions of normal respiratory epithelium. Early metaplasia is characterized by regions of low cuboidal and squamous epithelium; the surface epithelium flattens out, showing metaplasia of the stratified squamous type. After an interim period, during which the walls of columnar and basal cells are indistinguishable, the new type reaches its definitive form; high columnar cells show retrogression to cuboidal forms, whereas in sheltered areas under bony plates or generally in deeper parts of the cavities, the epithelium shows a tendency to increase in depth; short columnar or cuboidal cells become tall. Areas of vascular granulation tissue are overgrown by a layer of epithelial cells. In this way, after an initial transitional period, stratified squamous epithelium appears with the superficial cells flattened but not keratinized; finally, the stratified columnar epithelium is restored.

Regarding the olfactory cells, observations of Schultz and Gebhardt [22] indicate the possibility of partial restoration with regrowth of their dendritic and axonal processes. However, complete restoration, such as would allow the tissue to be compared closely with the normal state, is rarely attained. Under a detached olfactory epithelium, already a layer of regenerating cells appears. According to Smith,[23] the necrotic olfactory cells are enmeshed in regenerating cells derived from the nonsensory elements of the epithelium and then undergo gradual removal. All the cells may be destroyed, but only the nonsensory cells regenerate.

Knowlton and McGregor [20] reported that in dogs regeneration of the lining of the maxillary sinus after operative removal by curettage had occurred to such an extent that a normal mucoperiosteum appeared. Coates and Ersner [24] noted the reappearance of glandular tissue in the frontal sinus at a later period.

OBSERVATIONS

In comparing the anatomic elements of the nasal cavity of the rat with those of human nose as regards general disposition, some peculiarities seem to be of especial importance.

In the rat the entrance and the exit of the cavity are comparatively narrow. As a result, any material penetrating the nasal cavity will be

22. Schultz, E. W., and Gebhardt, L. P.: Studies on Chemical Prophylaxis of Experimental Poliomyelitis, J. Infect. Dis. **70**:7-50 (Jan.-Feb.) 1942.

23. Smith, C. G.: Changes in the Olfactory Mucosa and the Olfactory Nerves Following Intranasal Treatment with One Per Cent Zinc Sulphate, Canad. M. A. J. **39**:138-140 (Aug.) 1938.

24. Coates, G. M., and Ersner, M. S.: Regeneration of the Mucous Membrane of the Frontal Sinus After Its Removal (in the Dog), Arch. Otolaryng. **12**:642-648 (Nov.) 1930.

eliminated with greater difficulty. This may explain the fact that it takes longer to rid the cavity of pathologic accumulations. Some areas are especially devoid of adequate drainage. For instance, the posterior-superior-lateral corner: here, the first ectoturbinal, hidden behind the first and the second endoturbinal, faces a long and narrow canal between these two endoturbinals (figs. 3 *B, C* and *D;* fig. 5 *A*). This canal becomes easily blocked and locks up the first ectoturbinal, hindering the escape of secretions from the mucosal surface. This region becomes a dead end and acquires a kind of isolated pathology.

Another peculiarity is presented by the broad communication between the right and the left nasal airway. Immediately behind the vomeronasal organ the lower edge of the septum nasi dividing the two choanae is composed of a cartilaginous intumescence. The two choanae are almost facing each other, and in this way a communication is established between the two sides (fig. 3 *B*). The septal edge becomes connected with the lateral walls by two winglike or shelflike prolongations (terminal laminas) which form a second floor above the first as represented by the upper surface of the hard palate (fig. 3 *C* and *D*). Between the two floors a canal or duct is formed, representing the nasal orifice of the pharyngeal tube, a portion, which at its whole length runs under the septum of the ethmoidal half of the nasal cavity. The infraseptal portion of the pharyngeal duct as the initial part of the pharynx drains the anterior half of the nasal cavity, containing the nasoturbinal and the maxilloturbinal, and the posterior half, containing the ethmoturbinals—the first half conveying its secretions backward and the latter half forward, to reach the outlet. This situation accounts in great part for the distinctly separate pathologic involvements of the two portions. A more detailed investigation of these conditions is necessary.

In all our specimens the maxillary sinus was high and narrow, with its greatest width near the boundary of the anterior and posterior nasal portions. All over the wall is a continuous thick glandular layer which increases at the bottom to the enormous block of Stenson's gland. Between this block at the bottom and the adjacent part of the nasal cavity a constant dehiscence is observed. At this point, below the level of the sinus, the osseous lateral nasal wall is interrupted. The opening in the bone is covered outward by the glandular block, and inward by the mucosa of the nasal wall, which contains here a large venous sinus and a lymph follicle of considerable size (fig. 4 *C*). The dehiscence below the bottom of the sinus has no relation to the maxillary ostium.

Complete absence of frontal sinuses was noted in all 40 rats. The large marrow spaces of the frontal bone sometimes contained extravasated blood and pus.

Between the bottom of the nasal cavity and the dental alveoli direct communication was seen in the form of perforating vessels (fig. 4 *D*).

Fig. 3.—*A*, frontal section at the level of the vomeronasal organ.

B, frontal section at the level of the subseptal communication (region of the choanae).

C, frontal section showing the anterior part of the posterior half of the nasal cavity.

D, frontal section showing the posterior part of the posterior half of the nasal cavity.

In this figure *J* indicates Jacobson's organ; *S*, the nasal septum; *D*, the subseptal portion of the pharyngeal duct between the septum and the upper surface of the hard palate; *P*, the hard palate; *O*, the oral cavity; *MS*, the maxillary sinus; *NT*, the nasoturbinal; *MT*, the maxilloturbinal; *1* to *4*, the endoturbinals; *5* to *6*, the ectoturbinals.

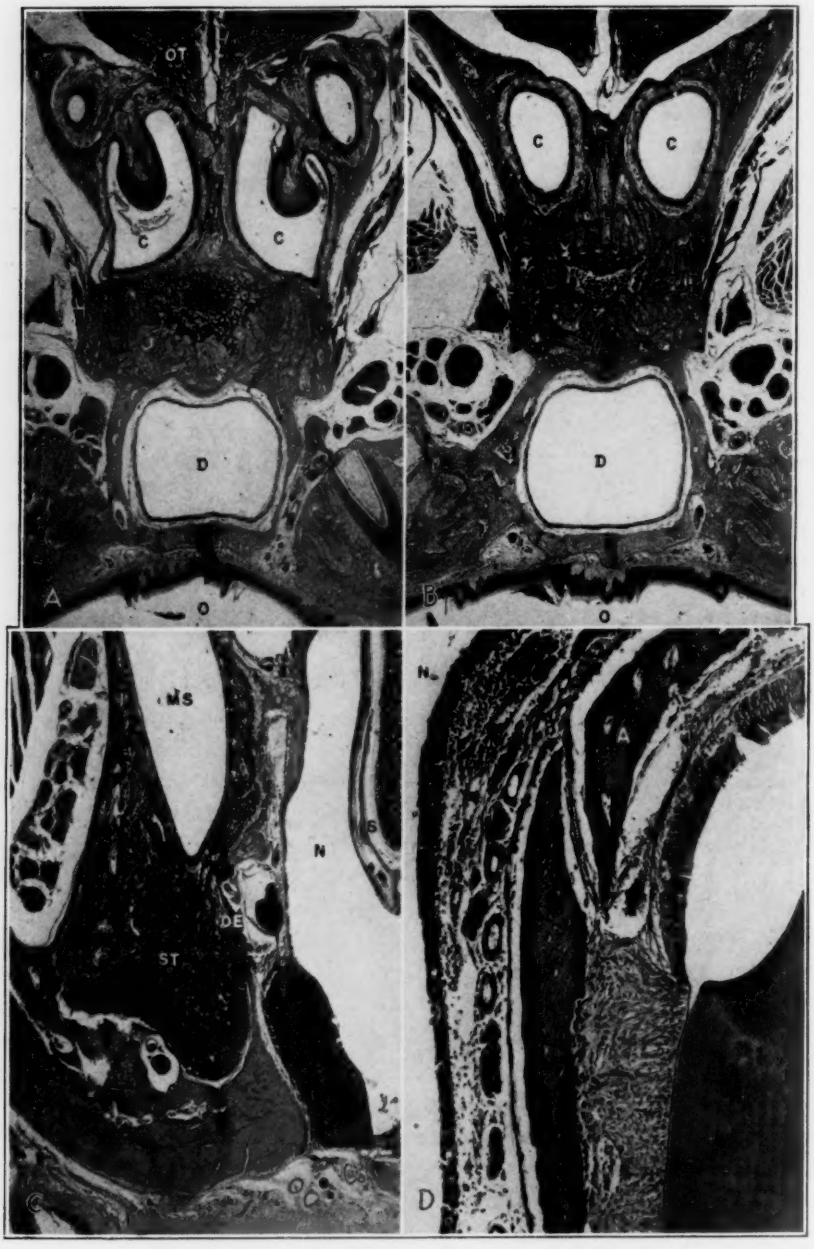

Fig. 4.—*A*, frontal section showing the posterior end (cul-de-sac) of the nasal cavity: *OT*, olfactory bulb; *CR*, cribriform plate; *C*, cul-de-sac with protruding end of the fourth endoturbinal; *D*, subseptal portion of the pharyngeal duct; *P*, hard palate; *O*, oral cavity.

B, frontal section showing the posterior outlet of the nasal cavity. The lettering is explained in *A*.

C, bottom of the maxillary sinus with large grandular block (Stenson's gland); dehiscence in the osseous nasal wall: *MS*, maxillary sinus; *ST*, Stenson's gland; *DE*, dehiscence; *N*, nasal cavity; *S*, nasal septum.

D, perforating vessel between the dental alveolus and the nasal cavity: *A*, alveolar wall; *N*, nasal cavity.

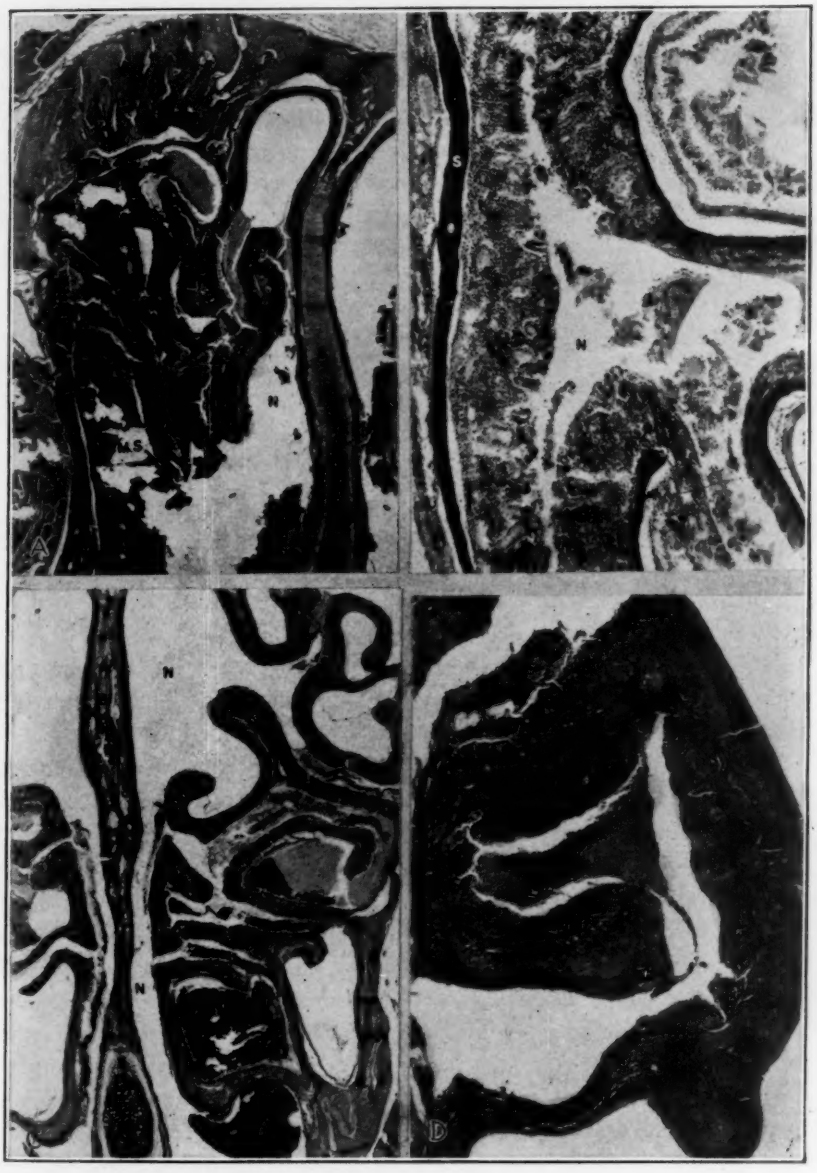

Fig. 5.—*A*, hemorrhagic-necrotic process in the nasal cavity and the maxillary sinus: *N*, nasal cavity; *MS*, maxillary sinus; *S*, septum.

B, suppuration with destruction of the mucous membrane of several endoturbinals: *N*, nasal cavity; *S*, septum.

C, hemorrhagic-necrotic process in the lower half of the ethmoturbinal region: *N*, nasal cavity; *S*, septum.

D, suppuration within the coil of an endoturbinal with infiltration of the mucous membrane on both sides of the turbinal bone.

In considering the pathologic findings in this series, we regarded the following as within normal limits and outside the realm of a definitely pathologic involvement: hyperemia, circumscribed, or involving larger areas; small extravasates within the tissues of the walls or free within the spaces bounded by the latter; fibrin lining the mucosal surfaces or filling the spaces. Only changes of this kind were present in 18 animals of the series. High grade local hyperemia was noted in 13 and diffuse in only 1. This is remarkable in view of the data summarized in the accompanying tabulation.

Pathologic Findings in the Nasal and Sinal Cavities of Rats

	Local	Diffuse
In the main cavity:		
Hemorrhage	3	1
Mucus, excessive quantity	1	2
Fibrin, excessive quantity	13	12
Suppuration	6	16
In the maxillary sinus:		
Hemorrhage	1	
Fibrin, excessive	6	
Suppuration	8	

In 2 of the 18 rats in which the main cavity was regarded as normal, pus was found in the maxillary sinuses.

Fibrin was designated as excessive on the basis of amount and unusual intensity of round cell activity noted around and within the meshes.

Among many others, the following additional pathologic changes were noted: abundance of goblet cells in large areas; cystlike empyemas between twin roots of turbinals; granulatory masses on the septum; formation of osteophytes by calcification of suppurative masses (fig. 6 *C*); foreign bodies, probably of plant origin, in the nose and the sinus with collateral reactions, such as hyperemia, edematous effusion and round cell accumulation in the surroundings (figs. 6 *D* and 7 *A* and *B*); debris. In 4 instances the choanae were completely blocked by pathologic products. A distinct isolated pathologic condition was frequently seen in the "dead angle," the posterior-superior-lateral corner. The mucosal lining was extensively infiltrated down to the basal layers or, with suppurative necrotic processes, there was even denudation of the bone in wide variations (fig. 6 *B*).

COMMENT

The short enumeration of anatomic peculiarities and distinct pathologic alterations observed in the nasal cavity and the maxillary sinuses in 24 of the 40 apparently healthy rats is self explanatory. These observations emphasize the difficulties encountered in the use of control animals. For example, the plan to use one nasal airway for experi-

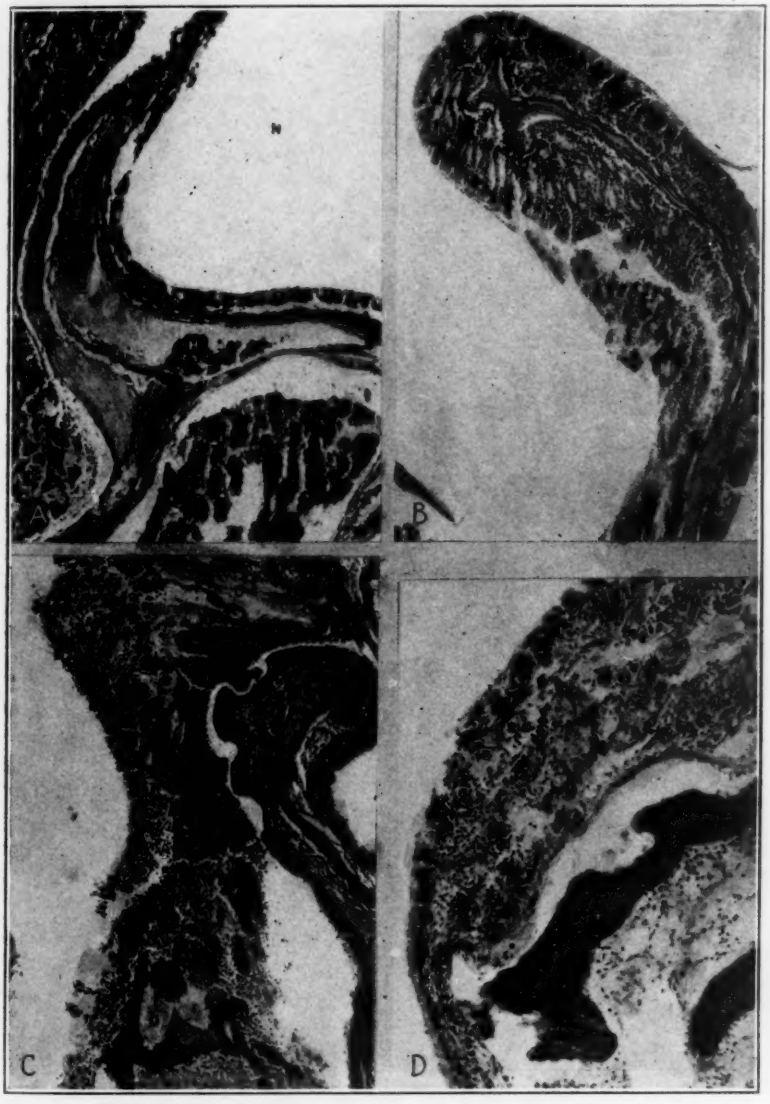

Fig. 6.—*A*, submucous effusion with hemorrhage at the bottom of the nasal cavity: *E*, homogeneous effusion; *H*, hemorrhage; *N*, nasal cavity.

B, abscess, with destruction of the mucosal lining of an endoturbinal and denudation of the turbinal bone: *A*, abscess.

C, suppurative mass around the nasoturbinal with calcification (osteophytes): *O*, osteophytes.

D, crystal-shaped foreign bodies (plant material) penetrating the mucous membrane of an endoturbinal, with suppuration.

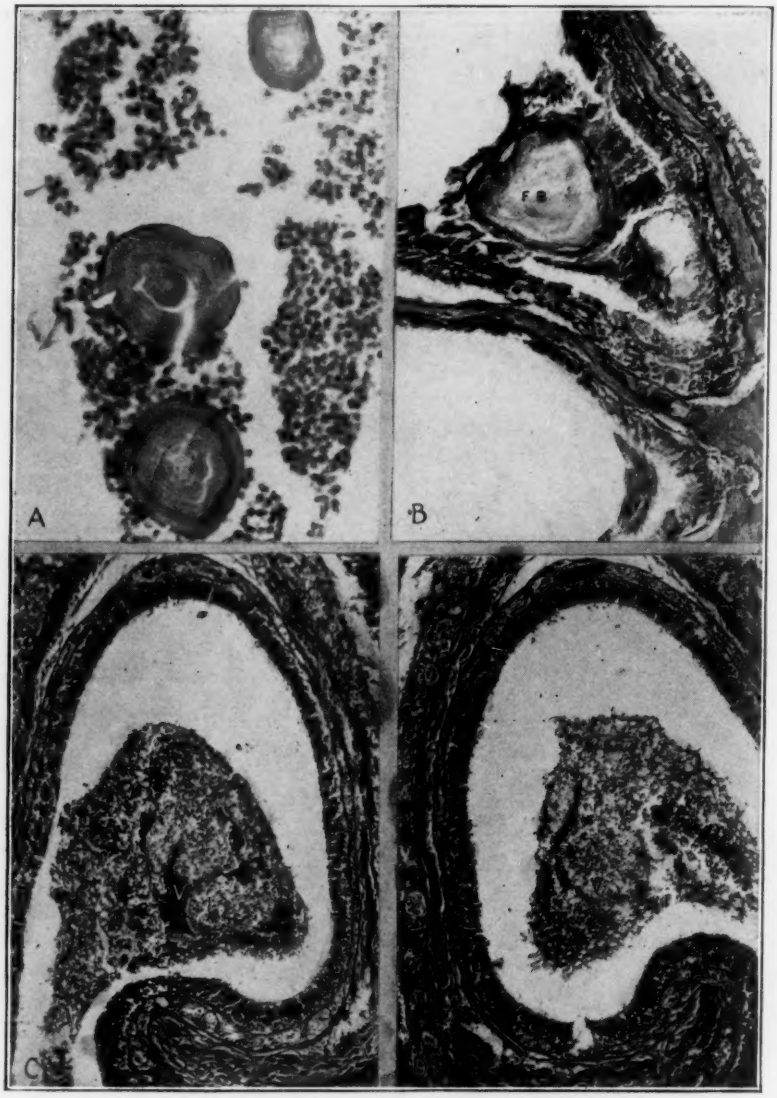

Fig. 7.—*A*, foreign bodies at the bottom of the maxillary sinus with round cell accumulation, resembling amylaceous or psammomabodies. (Colony of a non-pathogenic fungus?)

B, foreign body (plant material?) with reactive suppuration in the fork between two roots of an endoturbinal: *FB*, foreign body.

C, resorption of a hemorrhagic suppurative mass within a coil of an endoturbinal by vessels budding from the adjacent turbinal mucosa: *V*, branching vessel.

D, same as *C*, with further canalization of the suppurative mass: *V*, loop of a vessel.

ments while leaving the other intact for comparison is rendered illusory by the fact that a constant broad communication exists between the two nasal chambers in the anterior portion below the lower edge of the nasal septum, the choanae almost facing each other.

The most frequent artefact in connection with the histologic preparation is the separation of the soft tissue lining from the skeletal parts. Great caution is necessary before ablation (separation of the entire lining) or desquamation (separation of the epithelium from the underlying layers) may be regarded as produced by the experiment.

The inadequacy of clearance accounts for the frequency of foreign bodies tarrying in the cavities, with fully developed collateral reactions, the latter being evidence of their long stay. Of more consequence is the difficulty encountered in the elimination of pathologic secretions. On the other hand, the slower ventilation may be useful from the point of view of the macrosmatic analysis of the gaseous and liquid contents of the nasal cavities.

According to Waldapfel,[25] many of these changes may be produced without any specific destroying agent by simply putting cotton or gauze into the nose.

Most of the findings listed in the foregoing compilation from many sources and claimed to be produced experimentally were seen duplicated in these rats. Yet these animals might have been used freely as "controls," because they lived under entirely regulated conditions without previous experimental interference and seemed to be in perfect health. These changes have to be noted, as they can be easily confused with the effects of experimental procedures.

An intact peripheral olfactory organ is necessary in experimental investigations of psychologic phenomena. In this field of research the rat has acquired an increasingly important role. Among the experiments in question are those dealing with olfactory discrimination in general; in which discriminatory response with the help of olfactory cues is observed. The organ of smell is important in investigating certain special drives or in studying problem-solving behavior—for example, in the experiments of marking the true path of the maze with an olfactory trail. The results of experiments of this kind should not be declared valid until it is established by a postmortem histologic examination that at the time of the investigation the organs in question were functionally normal.

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25. Waldapfel, R., in discussion on Hunnicutt, L. G.: The Effect of Drugs on the Nasal Mucous Membrane, Tr. Pacific Coast Oto-Ophth. Soc. **29**:53-67, 1941.

SUMMARY

In considering the widespread use of laboratory animals in experiments with the nasal administration of drugs, it seemed advisable to collect data regarding the frequency of "spontaneous," nonexperimental pathologic changes which develop in seemingly healthy animals living without interruption in the laboratory where they were born.

Frontal sections of the nasal cavities of 40 rats of both sexes and of different age, weight and strain, originating from different laboratories and prepared by different technicians, were examined microscopically. Each of these animals might have been used as a "control," as they were apparently in good health; yet, with allowance of a wide margin for normal limits, pathologic changes were found in 24 animals (60 per cent). These changes duplicated a great variety of conditions, ranging from slight inflammation to the most severe destruction, which are frequently claimed to be produced experimentally.

A review of the literature revealed that these spontaneous pathologic changes are not fully appreciated. The anatomic peculiarities which have been emphasized in this study, together with the frequency of nonexperimental pathologic changes, warrant the utmost caution in evaluating findings that have been made by comparison with conditions in "blank" or " control" animals.

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THYROXIN THERAPY IN OTOSCLEROSIS

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THIS report summarizes the effects of thyroxin therapy as observed in 64 patients presenting clinical evidence of otosclerosis. Of these, 32 patients were treated according to the technic of Gray, while in 32 additional patients a different local anesthetic and a different preparation of thyroxin were employed for purposes of comparison.

The hypothesis that "the essential causative factor of otosclerosis is a gradually increasing defect in the vasomotor mechanism which governs the nutrition of the structures of the organ of hearing as a whole" was advanced by the late Albert A. Gray in 1934.[1] In his ingenious and convincing presentation it was pointed out that since the axon reflexes were included in the vasomotor mechanism and since the stimulus exciting the vasomotor mechanism was sound alone, it followed that the vestibular apparatus and the semicircular canals would be unaffected in otosclerosis. The deafness of persons with otosclerosis was regarded as largely functional, the result of insufficient blood being supplied to all the nerve structures concerned in the perception of sound. Gray denied that a defect of bone metabolism was present in otosclerosis. On the contrary, he pointed out that apart from their deafness such subjects are perfectly normal, with ordinary average health. He also emphasized the lack of evidence pointing to any defect in the endocrine glands or their secretions in otosclerosis.

In 1935 Gray[2] reported 14 cases in which otosclerosis and similar types of deafness were treated by local applications of thyroxin, with improvement in 7 cases. Thyroxin had been chosen solely on the basis of its local action and with full recognition that otosclerosis was not associated with a deficiency of the natural hormone of the thyroid gland. Gray regarded thyroxin simply as an agent which when applied locally produced active congestion in the contiguous blood vessels without producing inflammatory reactions due to irritant action.

Presented as a candidate's thesis to the American Laryngological, Rhinological and Otological Society June 16, 1941.

1. Gray, A. A.: The Otosclerosis Problem: Including Reports of Two Cases Pathologically Examined, Proc. Roy. Soc. Med. **27**:1179, 1934.

2. Gray, A. A.: The Treatment of Otosclerosis and Similar Types of Deafness by the Local Application of Thyroxine, Laryngoscope **45**:743, 1935; J. Laryng. & Otol. **50**:729, 1935.

Gray described the selection of suitable patients for treatment with thyroxin as follows:

> . . . When there is a noticeable loss of hearing for the lower notes, with retention for the high ones, associated with a negative Rinné, and with no serious diminution of absolute bone-conduction, along with absence, or only slight improvement, of the hearing on inflation of the middle ear, then the treatment by thyroxine injection may be tried. Cases in which the absolute bone-conduction is seriously diminished, even when the Rinné test is negative, are not likely to respond to treatment, and the same is true when there is any very noticeable loss of hearing for high notes.

He found that the appearance of the tympanic membrane gave little aid in the selection of suitable cases. He also stated that extreme deafness could not be expected to respond to the treatment

> . . . for in those cases the structural changes both in the region of the oval window and in the nerve-elements of the organ of hearing, have reached such an advanced stage that their capacity for functioning cannot be much affected by increased blood supply.

In Gray's series it was noted that when deafness was accompanied by tinnitus the latter symptom diminished or disappeared as the hearing improved. Paracusis was present in 4 cases in which there was hearing improvement. Return to functional activity of the ceruminous glands was observed in 2 cases. Usually four to eight days elapsed between the injection of thyroxin and the subjective improvement of hearing. The best results were obtained in patients between 18 and 30 or 35 years of age, but good results occurred in 2 patients aged 45 and 53 years. When hearing improved in the treated ear, improvement was apt to follow in the untreated ear as well.

Goldstein,[3] closely following the technic of Gray, found that

> . . . Of the forty-two cases subjected to thyroxine treatment, twenty-three or 54.8 per cent., have shown definite improvement in hearing capacity, and in some cases cessation or reduction of tinnitus and a general clarification in speech perception; ten, or 23.8 per cent., show slight improvement by comparison of audiograms before and after injection, but this was not stabilized in the final audiograms six months + later. In nine, or 21.4 per cent., no improvement was noted following treatment.

In no case did Goldstein observe a decrease in hearing following injections.

The criteria for the selection of patients for the study reported here were based on those described by Gray and Goldstein. They were essentially as follows: (1) a familial history of progressive deafness; (2) a defect in the upper and the lower tone limits, established by audio-

3. Goldstein, M. A.: Thyroxine in the Treatment of Otosclerosis: Preliminary Report, Laryngoscope **44**:112, 1936; Thyroxine Therapy in Otosclerosis: Report of 42 Cases, J. Laryng. & Otol. **53**:444, 1938; Laryngoscope **48**:443, 1938.

metric and tuning fork tests; (3) a negative Rinne test; (4) patulous eustachian tubes; (5) a relatively normal membrana tympani; (6) tinnitus; (7) paracusis Willisiana; (8) a progressive decline in hearing; (9) a degree of deafness not sufficiently extreme to indicate structural changes not amenable to increased blood supply.

The technic employed in the treatment of 32 patients was identical with that of Gray and of Goldstein. From 15 to 20 drops of an aniline solution of cocaine hydrochloride [4] were placed in the external auditory canal. The solution was permitted to remain for five minutes, and then the canal and the drum head were thoroughly dried. A large cork placed between the upper and lower jaws of the patient presumably prevented the escape of the thyroxin solution by way of the eustachian tube. A 1/64 (0.001 Gm.) grain tabloid of thyroxin was then dissolved in four drops of warm sterile distilled water, and the resulting solution was drawn into a tuberculin syringe fitted with a needle bent to the form of a bayonet. The needle was longer than the external auditory canal and possessed a short bevel. It was inserted midway between the tip of the handle of the malleolus and the posterior rim of the annulus tympanicus. The patient, with jaws well separated by the cork, assumed the upright position just as soon as the injection had been completed. The upright position was held for at least three minutes. Four consecutive injections were made alternately in the right and left ears at intervals of a week; thus fourteen days were allowed for each ear to absorb the thyroxin solution. (Gray suggested that two or three additional injections might be necessary throughout the year.)

With 32 additional patients, a different local anesthetic was substituted for the aniline–cocaine hydrochloride, and a different thyroxin preparation was substituted for the tabloid thyroxin, but in all other respects the technic employed was similar to that used with the first group. These exceptions to the original technic will be noted in the tables and in the comment.

Of the 64 patients included in this study, 47 were between 19 and 34 years of age, while 17 were between 37 and 61 years of age. This grouping was suggested by Gray's statement that thyroxin therapy was of little value for persons over 30 or 35 years of age.

Of 47 otosclerotic patients under 35 years of age, 32 received tabloid thyroxin under cocaine hydrochloride–aniline anesthesia according to the technic of Gray and Goldstein, while 15 patients received ampule thyroxin [5a] under phenol-cocaine-menthol [5b] anesthesia.

4. Chemically Pure aniline 90 parts, cocaine hydrochloride 10 parts.

5. (*a*) This solution, known as thyroxin solution 0.4 per cent (Roche-Organon), was prepared for the purpose of being used experimentally in the

(Footnote continued on next page)

Audiometric records were made for each patient twenty-four hours after each injection and at forty-eight hour intervals for two weeks after the last injection. Thereafter monthly records were made up to six months.

Table 1 presents in condensed form some results of thyroxin therapy in 32 patients under 35 years of age. Of these, 9 were males and 23 were females.

Only 4 of the 32 patients in this group were definitely convinced of improvement of hearing. The improvement was noted by these patients five to ten days after the first injection. Some improvement was shown in the hearing level of each of them by audiometric tests, but the improvement in individual ears varied only from 4 to 11 decibels over

TABLE 1.—*Effects of Tabloid Thyroxin and Cocaine Hydrochloride–Aniline Anesthesia in Thirty-Two Patients Under 35 Years of Age with Clinical Manifestations of Otosclerosis*

Age		19	20	21	22	24	25	26	28	29	30	32	33	34	Total
Patients		2	2	4	3	2	2	4	2	3	2	1	3	2	32
Subjective improvement		0	0	1	0	0	1	0	0	0	1	0	1	0	4
Effect on tinnitus		0	0	0	0	0	0	0	0	0	0	0	0	0	0
Net change shown by audiometer after last injection	+	1	1	1	1	0	1	2	0	1	1	0	1	1	11
	0	0	1	2	1	1	0	1	1	1	1	1	2	0	12
	—	1	0	1	1	1	1	1	1	1	0	0	0	1	9
Improvement shown by audiometer six months after last injection		0	0	0	0	0	0	0	0	0	0	0	0	0	0
															Average "gain" in decibels
Gain in decibels in "improved" patients 24 to 72 hours after last injection *	R. ear	7	6	4	4	..	11	6,7	..	6	5	..	5	7	6
	L. ear	5	5	7	8	..	8	5,4	..	3	8	..	9	3	5
															Average "loss" in decibels
Decibel change in patients showing "loss" 24 to 72 hours after last injection *	R. ear	9	..	6	8	9	4	7	5	7	..	..	..	15	7
	L. ear	7	..	7	5	13	6	8	6	4	..	..	..	12	7

* Through the tonal range of 62 to 8192 cycles.

the tonal range of 64 to 8192 cycles. The average gain over this tone range was between 6 and 7 decibels.

Eleven of the 32 patients were shown to have some improvement by audiometric estimations made forty-eight hours after the last injection. No significant alterations of the acoustic level were noted after this interval. The average gain per ear over the tonal range of 62 to 8192 cycles in the 11 patients was 5 to 6 decibels. Twelve other patients failed to show any variation in the hearing level of either ear beyond plus or minus 3 decibels after two injections in each ear. Nine other

treatment of otosclerosis. The composition is described as follows; crystalline synthetic thyroxin in a menstruum consisting of sodium hydroxide solution, dihydroxyethylamine and distilled water. The solution had a p_H of about 9.6. (*b*) A fluid resulting from the admixture of equal parts of phenol, menthol and cocaine (alkaloid) was used.

patients showed an average loss of 7 decibels per ear following two injections in each ear. Thus while a gain of 5 to 6 decibels per ear occurred in 11, or 34.3 per cent, of the patients, in 21, or 65.6 per cent, of the patients there was no change or actually a slight diminution of hearing.

All 32 patients failed to show any improvement after the lapse of six months; even the 11 patients exhibiting slight temporary improvement had hearing levels as low or lower than before undergoing treatment. It was noted with some interest that the introduction of tabloid thyroxin into the middle ear failed to depress the hearing level as determined by audiometric tests to the extent one would expect in at least an occasional case.

TABLE 2.—*Effects of Ampule Thyroxin and Cocaine-Phenol-Menthol Anesthesia in 15 Patients Under 35 Years of Age with Clinical Manifestations of Otosclerosis*

Age		20	21	22	23	26	27	28	30	31	32	33	34	Total
Patients		1	1	1	1	3	1	1	1	1	1	1	2	15
Subjective improvement		0	0	0	0	1	0	0	1	0	0	1	0	3
Effect on tinnitus		0	0	0	0	0	0	0	0	0	0	0	0	0
Net change shown by audiometer after last injection	+	0	1	1	0	1	0	1	0	0	0	1	1	6
	0	1	0	0	0	0	1	0	0	0	1	0	0	3
	—	0	0	0	1	2	0	0	1	1	0	0	1	6
Improvement shown by audiometer 6 months after last injection		0	0	0	0	0	0	0	0	0	0	0	0	0
														Average "gain" in decibels
Gain in decibels in "improved" patients 24 to 72 hours after last injection *	R. ear	..	8	5	..	4	..	7	..	..	..	3	9	6
	L. ear	..	4	6	..	6	..	5	..	..	..	5	7	5
														Average "loss" in decibels
Decibel change in patients showing "loss" 24 to 72 hours after last injection *	R. ear	..	..	..	7	7,6	..	..	12	3	..	..	8	7
	L. ear	..	..	..	9	5,8	..	..	10	7	..	..	9	8

* Through the tonal range of 62 to 8192 cycles.

No relief of tinnitus could be established in any of the 32 patients. Since the tinnitus is entirely a subjective manifestation, no leading questions were asked, and not a single patient volunteered the information that tinnitus had in any way abated.

The results obtained by the use of ampule thyroxin and cocaine-menthol-phenol anesthesia in 15 patients under 35 years of age are condensed in table 2. This group consisted of 4 males and 11 females. The only variation in technic consisted in the substitution of a different thyroxin preparation and a different local anesthetic.

Three patients in this group reported subjective improvement of hearing, but audiometric examination revealed but slight change in 2 (average of 5 decibels in individual ears) and a slight loss in 1. Six patients (40 per cent) showed an average gain of 5 to 6 decibels per ear over the tonal range of 62 to 8192 cycles, while 9 patients showed

no change or slight lowering of the acoustic level after two injections in each ear. Tinnitus was not relieved in any of the 15 patients. None of the 15 patients showed improvement in the acoustic level six months after the final injection.

The results obtained by the use of ampule thyroxin and phenol-menthol-cocaine anesthesia in 17 patients over 35 years of age are condensed in table 3. This group contained 4 males and 13 females.

Four patients in this group reported subjective improvement in hearing, but only 1 of these presented evidence of some change for the better in audiometric tests, a gain of 9 decibels in one ear and 6 decibels in the other over the tonal range of 62 to 8192 cycles.

TABLE 3.—*Effects of Ampule Thyroxin and Cocaine-Phenol-Menthol Anesthesia in Seventeen Patients over 35 Years of Age with Clinical Manifestations of Otosclerosis*

Age		37	39	40	43	46	47	48	51	52	55	58	61	Total
Patients		1	2	2	1	3	1	1	1	1	2	1	1	17
Subjective improvement		0	2	0	0	1	0	0	0	0	0	1	0	4
Effect on tinnitus		0	0	0	0	0	0	0	0	0	0	0	0	0
Net change shown by audiometer after last injection	+	1	0	1	0	1	1	1	0	0	1	0	0	6
	0	0	1	1	0	0	0	0	1	0	0	1	1	5
	—	0	1	0	1	2	0	0	0	1	1	0	0	6
Improvement shown by audiometer 6 months after last injection		0	0	0	0	0	0	0	0	0	0	0	0	0
														Average "gain" in decibels
Gain in decibels in "improved" patients 24 to 72 hours after last injection *	R. ear	7	..	6	..	9	3	6	..	..	8	..	..	6
	L. ear	5	..	7	..	6	5	7	..	..	6	..	..	6
														Average "loss" in decibels
Decibel change in patients showing "loss" 24 to 72 hours after last injection *	R. ear	..	5	..	7	12,8	..	..	..	7	4	..	..	7
	L. ear	..	6	..	9	10,6	..	..	..	5	6	..	..	7

* Through the tonal range of 62 to 8192 cycles.

Of the 17 patients, 6 (35.2 per cent) showed an average gain of 6 decibels per ear over the tonal range of 62 to 8192 cycles after two injections in each ear, while 11 patients (64.7 per cent) showed no change or a slight diminution of hearing under the same circumstances. No effect on the intensity of tinnitus was evidenced in any of the 17 patients. Audiometric examination after the lapse of six months failed to establish improvement of hearing in a single patient.

Livingston and co-workers [6] had suggested a possible advantage in the use of the suspension of solid particles obtained by agitating tabloid thyroxin with 4 or 5 drops of distilled water, in that the particles might act as a reserve supply of the drug or as a foreign body causing further congestion. A comparison of the effects of tabloid thyroxin on the

6. Guthrie, D.; Livingston, G., and Suggitt, S. C.: Discussion on Intratympanic Medication, with Special Reference to Thyroxine, Proc. Roy. Soc. Med. **29**:1691, 1936.

patients included in table 1 and the effects of ampule thyroxin on the patients included in tables 2 and 3 failed to show an appreciable difference in the action of the two preparations in irritant action, production of pain or effect on the hearing level.

The 32 patients grouped in table 1 received cocaine hydrochloride–aniline as a local anesthetic, while the 32 patients grouped in tables 2 and 3 received a cocaine-phenol-menthol mixture for this purpose. Both preparations produced satisfactory local anesthesia, but the cocaine-phenol-menthol mixture required two to three times as long to produce good anesthesia as did the cocaine hydrochloride–aniline oil.

The effect of thyroxin therapy in patients under 35 years of age did not appear to differ from the effect in those over 35 years of age. In each group the influence on the hearing level was negligible.

Sixty-four patients received two injections of the drug in each ear, a total of 256 injections, without infection in a single instance. This confirms the reports of Gray and Goldstein as to the relative safety of the procedure in this respect. No effect on the secretory activity of the ceruminous glands could be established in any of the 64 patients.

COMMENT

Suggitt [7] treated 11 patients who had the characteristic symptoms and signs of otosclerosis by introducing isotonic solution of sodium chloride by way of the eustachian tube into the middle ear cavity. Three of these patients showed an improvement in hearing comparable to that in a series of patients treated by tympanic injection.[6] He observed 15 otosclerotic patients for periods up to twenty-two months with the audiometer in a soundproof room and found the average variation for the range 256 to 2048 cycles to be about 10 decibels. Since comparable figures had been given for series treated by eustachian injection and by intratympanic injection and for 3 patients with nerve deafness, he felt that the improvement of hearing in these patients could not be placed outside the limits of normal variation. He concluded that no treatment for otosclerosis could be considered of value unless it could produce a sustained improvement in hearing appreciably greater than 10 decibels over the greater part of the tonal range of 64 to 8192 cycles.

Bunch [8] concluded on the basis of his studies that changes greater than plus or minus 5 decibels, or 7.5 decibels at the most, must be considered significantly greater than gains due to the attention factor.

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7. Suggitt, S.: Observations on the Variation in Hearing in Otosclerosis, J. Laryng. & Otol. **53**:294, 1938.

8. Bunch, C. C.: The Progress of Deafness in Clinical Otosclerosis, Laryngoscope **49**:793, 1939.

If one accepts these criteria, the range changes in the hearing levels of the 64 patients included in this study failed to exceed the variations known to occur without treatment of any sort or to differ greatly from variations due to the attention factor. In 23 of the 64 patients slight improvement was shown in audiometric tests made twenty-four to seventy-two hours after the last injection, but in only a single ear was this gain as much as 11 decibels throughout the tonal range of 62 to 8192 cycles, and the average gain per ear was but 5 to 6 decibels. Even this slight improvement was transient, and no sustained improvement of the hearing could be demonstrated after the lapse of six months.

It is difficult to reconcile oneself to a technic which entails repeated puncture of the tympanic membrane, a procedure not without risk in spite of the infrequency of infection when it is performed by capable hands. The further injecting of thyroxin into the middle ear two or three times a year does not appear to be justified by the transient and somewhat dubious effects noted in the otosclerotic patients included in this study.

CONCLUSIONS

1. Cocaine hydrochloride–aniline [4] is superior to cocaine-phenol-menthol mixture [5b] only in its more rapid action in producing local anesthesia of the tympanic membrane.

2. The effects of tabloid thyroxin dissolved in distilled water do not appear to differ from the effects of thyroxin obtained in sterile solutions in ampules when these preparations are introduced into the middle ear.

3. Intratympanic injection of medicaments can be accomplished with comparative safety, but the end should justify the means.

4. Thyroxin introduced into the middle ear cavities of 64 persons with clinical manifestations of otosclerosis failed to effect alterations in the hearing level which were in excess of the normal variation of the hearing level in otosclerosis.

1912 Spruce Street.

ODONTOMA OF THE NASOPHARYNX

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AS LONG ago as 479 B. C. Herodotus described a skull found in the battle of Plataea, in which each jaw contained teeth that were fused in a mass. Centuries later, in 1774, an osseous tumor of the mandible was reported, and again in 1778 three dentigerous cysts were described. It was not until 1869, however, that Broca coined the word "odontoma." The root is Greek, from the words *οδους-οδοντος* (tooth) and *ωμα-ωματος* (tumor). At a meeting of the Anatomic Society in Basel, Switzerland, in 1895, the term "odontoma" was adopted officially and added to the existing medical nomenclature.

The odontoma has been variously defined by many authors as "an abnormality with increased tissue, derived from the dental formative organs" (Sprawson [1]); as a "benign tooth tumor consisting of enamel, dentine and cementum either alone or in combination" (Gullifer [2]); as "two or more malformed teeth fused together," British Dental Association. It should be borne in mind, however, that if the word "odontoma" is to be accepted literally, the anomaly itself must be in effect both tooth and tumor. Bass [3] pointed out that a supernumerary tooth, which has been called an odontoma, may not be classed as such, nor may pearls and nodules, since they have a definite limit and pattern, whereas a tumor has been designated as "a new growth of cells which proliferate without control, serve no useful function and have no definite termination."

As a matter of fact, a great deal of confusion has existed as to what is and what is not a true odontoma. This was clarified somewhat in 1914, when the British Dental Association compiled a classification consisting of three main groups. This association placed odontomas in three categories—(1) epithelial odontomas, (2) composite odontomas and (3) connective tissue odontomas—and suggested subclassifications under each heading. But even this classification was not accepted by all investigators.

Presented as a candidate's thesis to the American Laryngological, Rhinological and Otological Society.

1. Sprawson, E.: Definition of an Odontome, Brit. Dent. J. **50**:775, 1929.
2. Gullifer, W. H.: Odontoma, Am. J. Orthodontics **24**:795, 1938.
3. Bass, P. B.: Odontomas, Dent. Digest **49**:446, 1943.

Perhaps the simplest and best classification to date has been offered by Thoma,[4] who said that tumors of odontogenic origin are composed of one or more tissues of the normal tooth, and further classified them as: (1) those formed from epithelial cells (epithelial odontomas), (2) those in which no tooth substance is produced (soft odontomas), (3) those with development and calcification of intercellular structures (hard odontomas) and (4) those in which both epithelial and mesenchymal derivatives appear (composite odontomas). These four classifications may be subdivided broadly as follows:

EPITHELIAL ODONTOMAS	Follicular cysts Adamantine epitheliomas Enameloma
MESENCHYMAL ODONTOMAS	Soft odontomas Calcified simple odontomas
MIXED ODONTOMAS	Soft mixed odontomas Calcified mixed or composite odontomas

For the purposes of thorough study these broad classifications may be subdivided again, but I feel that this is unnecessary here. Although throughout the history of the odontoma, its classifications, its subdivisions, and even in the suggestion and the rejection of its name there has been much disagreement by investigators, on one point—so far as the literature reveals—they agree: The true odontoma is benign.

"Epithelial odontomas, as the name implies, are the result of abnormal development in the epithelial elements alone. Composite odontomas are tumors containing both epithelial and mesoblastic tissue" (Malone [5]). A brief description of the various types in the latter group will be an aid in classifying the case to be reported here. The calcified tumor is usually seen early in life, in either sex. as a slow growing, painless swelling. It is usually associated with unerupted teeth and occurs in the molar region of either the mandible or the maxilla. The tumor is an encapsulated calcified structure containing enamel, dentin and cementum. The complex composite odontoma is characterized by a conglomerate mass of calcified tooth structure composed of enamel, dentin and cementum. The compound composite odontoma, on the other hand, is an encapsulated tumor containing numerous teeth, portions of teeth or denticles.

Thoma [4] pointed out that the odontoma may appear at any place in the jaws but is most commonly seen in the region of the mandibular third molar; it is said to occur in more males than females. The literature is replete with reports of odontomas having been found in

4. Thoma, K. H.: Oral Pathology, St. Louis, C. V. Mosby Company, 1941, pp. 948-960.

5. Malone, L. A.: Odontomas with Case Report, Radiology **34**:573, 1940.

various sites in the jaws, the anomaly being peculiar to that region. Stout,[6] however, saw 752 tumors of the nose, throat and larynx, with but 47 in the nasopharynx. These are all described as being malignant, and in no sense may they be classified as odontomas. Thus it becomes evident that any tumor of the nasopharynx is uncommon, but a true odontoma of that area is rare indeed, and—so far as could be learned by a careful search of the literature—an odontoma of the nasopharynx has never before been adequately described.

This may well be because the nasopharynx is not an easy site to examine. Such an examination requires the utmost care and a thorough knowledge of the structures involved. The posterior wall of the nasopharynx is formed by the anterior surfaces of the upper cervical vertebrae, while the basilar process of the sphenoid bone forms the roof. Anteriorly it communicates with the posterior choanae, where the posterior border of the septum and the tips of the turbinates are visualized. The posterior surface of the soft palate forms the anterior border. Communication below is with the oropharynx. On the lateral aspect of the nasopharynx, one views the pharyngeal opening of the eustachian tube, the eustachian eminence and the pharyngeal recess. Lateral to the lateral pharyngeal wall, one encounters the posterior fossa of the pharyngomaxillary space, bounded as follows: anteriorly, by the neck and the ramus of the mandible; posteriorly, by the mastoid and styloid processes; inferiorly by the posterior belly of the digastric muscle. The fossa extends upward to the external auditory meatus, and it is prolonged downward into the carotid triangle.

The enumeration of fundamental points may sound unimportant, but the nasopharynx is one of the most neglected areas in the field of otorhinolaryngology. Carmody [7] referred to it as "The Epipharynx—The Unknown in Otolaryngology." Bringing it to attention periodically may lay emphasis on its importance, and impress on physicians the value of a less neglected and less hurried examination of this area.

Coates,[8] in describing some of the difficulties encountered in an examination of the nasopharynx, pointed out that the curtain of the soft palate, in such close proximity to the posterior wall, often obstructs one's direct view except where it has been destroyed or there is a congenital cleft—in which case an ample view may easily be obtained. The pharyngeal reflexes are extremely active in almost every one, and gagging results from the lightest touch on the velum palati or the

6. Stout, A. P.: Symposium on Nasopharyngeal Tumors: Pathological Diagnosis, Laryngoscope **51**:446, 1941.

7. Carmody, T. E.: The Epipharynx—The Unknown in Otolaryngology, Tr. Am. Acad. Ophth. **45**:255, 1939.

8. Coates, G. M.: The Nasopharynx, Arch. Pediat. **60**:10, 1943.

pharyngeal wall. Gagging is frightening and unpleasant, and the importance of the psychologic approach is not the least important feature of a rhinologic examination.

In spite of difficulties, a complete examination of the nasopharynx should be made in all cases. This is usually made by reflecting light on a rhinoscopic mirror, held back of the soft palate. Portions of the nasopharynx may be seen by anterior rhinoscopy. In young children it is often necessary to palpate the area to determine the presence and the origin of a postnasal growth. Examination may also be made with a pharyngoscope passed into the nasopharynx through the nose. General anesthesia may be finally resorted to.

Hypertrophied lymphoid tissue is commonly found in the pathologic nasopharynx, and its presence produces nasal and aural symptoms. Sometimes the optic nerve suffers, but the first cranial or olfactory nerve is seldom affected. Titrud and Peyton [9] reported that there may be a disturbance of taste sensibility "because of the tumor affecting the mandibular branch of the fifth or the chorda tympani in the seventh nerve." The motor branches of the nerve are involved much less frequently than the sensory.

Tumors of the nasopharynx are relatively infrequent. Stout [6] found in a series of 70,000 tumors only 32 nasopharyngeal tumors, mostly malignant. Those of the jaws—true odontomas—are seen more frequently. The benign neoplasms include the fibroma, the hemangioma, the papilloma, the lipoma, the osteoma and the teratoma. The malignant tumors include the carcinoma, the sarcoma and the malignant chordoma. As to cysts and retention abscesses of the nasopharynx, Kully [10] stated that of 88 patients, 22 presented no subjective symptoms referable to the nose or the throat, and discovery of the cyst or the abscess was made on routine examination. The importance of a thorough examination cannot be stressed too often.

The occurrence of an odontoma during the period of first dentition is uncommon Hatton [11] reported, and Jacobs [12] found no odontoma where a full set of erupted teeth was present unless an impacted or a malposed supernumerary occurred.

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9. Titrud, L. A., and Peyton, W. T.: Nasopharyngeal Tumors and Their Neurological Complications, J. Nerv. & Ment. Dis. **92**:727, 1940.

10. Kully, B. M.: Cysts and Retention Abscesses of the Nasopharynx: Eighty-Eight Cases, Tr. Am. Laryng., Rhin. & Otol. Soc. **40**:185, 1934.

11. Hatton, E. H.: An Unusual Odontoma, Tr. Chicago Path. Soc. **13**:448, 1932.

12. Jacobs, M. H.: Etiology of Dentigerous Cysts, Multiocular Cysts, Odontomas and Adamantinomas, Am. J. Orthodontics (Sect. Oral Surg.) **25**:1190, 1939.

Bleeding and obstruction, deafness, tinnitus, otitis media, mastoiditis and sinusitis may be present in patients with nonmalignant nasopharyngeal tumors. Hemorrhage causing fatal loss of blood has been reported. Malignant tumors of the nasopharynx are insidious. Often they have invaded the neighboring cervical lymph nodes, with metastases resulting, before attention is called to them.

Diagnosis of odontoma is relatively simple. A history carefully taken, a physical examination, a consideration of age and the rate of growth are helpful. Roentgen examination with reference to the jaw is conclusive; in this area an encapsulated tumor entirely separate from the adjacent bone is demonstrable, with or without tooth structure. On the other hand, one is not able to make a positive diagnosis of odontoma of the nasopharynx until after the removal of the tumor.

Differential diagnosis of malignant and benign types is comparatively easy even without histologic procedures, since the classic signs of each type in its more advanced stage have been well established. However, early attention to any type of tumor is extremely important.

Differential diagnosis of odontoma of the nasopharynx is quite limited. The few lesions requiring consideration are fibroma, sarcoma, osteoma, teratoma and periosteal lesions. If tooth elements are evidenced by roentgen examination, the only condition to be differentiated is teratoma, and this would be discovered at operation and pathologic examination.

Excision is the treatment of choice in the presence of benign tumors, as well as in those cases in which the tumor is suspected or is definitely known to be cancerous. A biopsy specimen should be taken when possible, and laboratory procedures instituted to determine the nature of the tumor.

The treatment of the odontoma is complete enucleation of the tumor and capsule. An intraoral or an external approach, I think, may be chosen. The fibroma, as a rule, is removed by the intranasal or the transantral route. Owing to the lack of proper intraoral visualization of the deeper portion of the lateral wall of the nasopharynx and the impossiblity of the transantral route it may be considered possible to approach an odontoma by the external route through the posterior pharyngomaxillary space.

Full and complete removal is imperative. In cases in which there is a possibility of the surrounding tissue being involved the cosmetic effect should never be weighed against the value of complete eradication of the growth. A careful follow-up, with inspection of the surrounding areas and lymph nodes, should be made to ascertain the possibility of recurrence. In true odontoma recurrence is rare; nevertheless, it does occur, as will be seen in the case now reported:

REPORT OF A CASE

B. N., a girl aged 12, was first examined by me on Feb. 2, 1934. She complained of a growth in the throat.

About five and a half years before this, while her tonsils and adenoids were being removed, a firm growth was discovered in the pharynx by the operating surgeon. It was kept under observation rather closely for three years without any appreciable increase in size being noted. At the time of my examination she had some difficulty in hearing with the left ear and her speech was somewhat thickened. She frequently had sore throat, but no actual pain referable to this growth. There was no history of abscessed ears. The general health was good. The appendix had been removed two years before. She had had the usual children's diseases, with good recovery.

Physical Examination.—The tonsils had been removed. The nasopharynx showed no adenoids. There was a large growth on the left lateral wall in the region of the orifice of the eustachian tube, suggestive of fibroma. It seemed attached to the left lateral wall. The mass had a bony feel and was quite fixed. The nose and sinuses appeared entirely normal except for a somewhat pale mucosa on the left side, the condition of which was apparently due to postnasal obstruction. The right ear was normal; the left ear had a thickened tympanic membrane with marked retraction. The neck contained no palpable glands. The larynx and the hypopharynx appeared entirely normal.

Roentgen Report.—The left lateral views of the neck showed a tooth, apparently a molar tooth, in the left posterior area of the pharynx. Its crown projected directly posterior. It did not appear attached to any bone. There was slightly increased density around it, probably due to remnants of the tooth bud.

As the roentgenograms were not kept, it is impossible to reproduce them.

A diagnosis of nonmalignant embryonic bony tumor was made and its removal advised.

Surgical Procedure and Observations.—On February 28, with the patient under general anesthesia, the tumor was removed through the intraoral route without incident.

A large bony cellular tumor, covered with dense fibrous tissue, was found in the left lateral pharyngeal space about 2 inches long by 1 inch wide (5 by 2.5 cm.), apparently not attached to any bone. A deciduous tooth lay firmly embedded in the most lateral portion of the growth, firmly fixed in the bony cellular tissue, just below and internal to the tip of the mastoid process. Little bleeding was encountered throughout the operation. An attempt was made to snare the tumor completely; but, because of its size and inaccessibility, it had to be removed in sections. It was apparent that a very small portion of the bony tumor was left laterally at the site of the embedded tooth. It was not possible to determine any attachment of the growth.

The postoperative diagnosis was: embryonic bony tumor with a deciduous tooth, double rooted, embedded in an abnormal socket posterior and internal to the left posterior ramus of the mandible.

Pathologic Report.—Gross Description: The submitted specimen consisted of a mass of tissue and a tooth removed from the postnasal region. The tooth appeared to be somewhat of a formed bicuspid with a lower portion shaped like a fish hook. Surrounding this was a lobular mass of tissue measuring 3 by 3 by 2 cm., appearing encapsulated, having a thick fiber-epithelial wall and con-

taining cancellous bone. The wall itself measured from 3 to 8 mm. in thickness. It was rich in chronic granulation tissue and fibrous tissue, and the cancellous bone was moderately friable, fairly easily disintegrated.

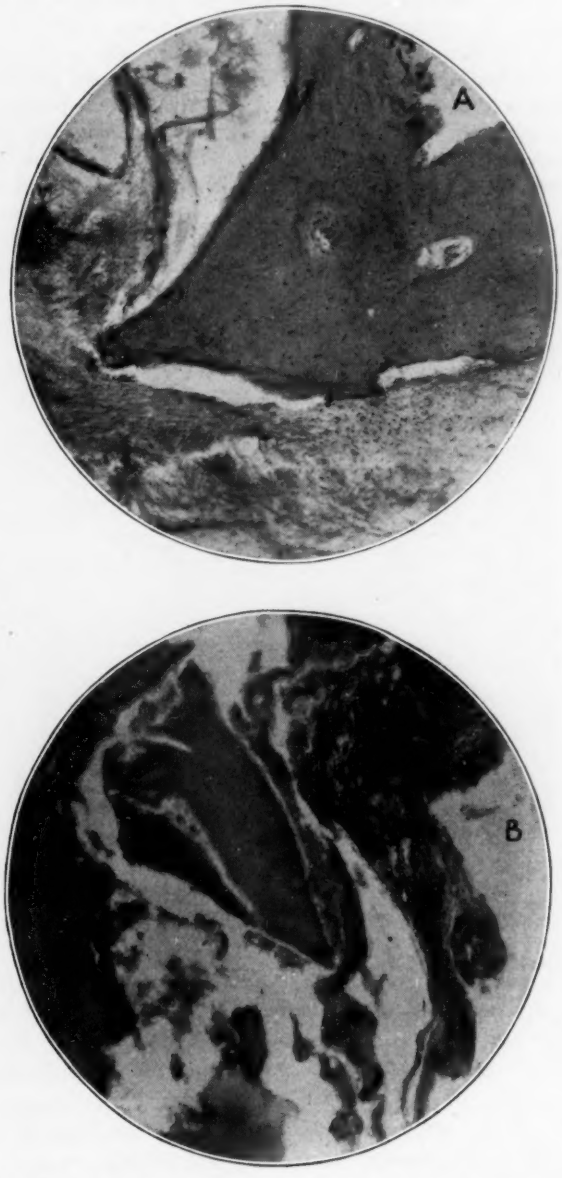

Fig. 1.—*A*, photomicrograph of the specimen of tumor removed in 1934. *B*, photomicrograph of the specimen of tumor removed in 1942.

Microscopic Description (sections taken through the wall and through the bony tissue for microscopic study): The sections showed the mass described

to be lined by a flattened, somewhat atrophic but otherwise not unusual squamous cell mucous membrane. In some areas there was a moderate amount of hypertrophy, but the rete pegs were not unusual, and the basement membrane was intact. The sections through the wall showed old fibrous tissue in various stages of degeneration. There were also some elastic fibers within the wall. The degeneration of the fibrous tissue ranged from collagenous to hyaline, with some areas of calcification and many spicules of bone. The lesion probably originated on the basis of a congenital rest, with degeneration and hypertrophy occurring as a result of a foreign body reaction. A few small foreign body giant cells and a few inflammatory lymphocytes were seen. There was nothing suggestive of cancer or precancerous degeneration. The lesion should not recur.

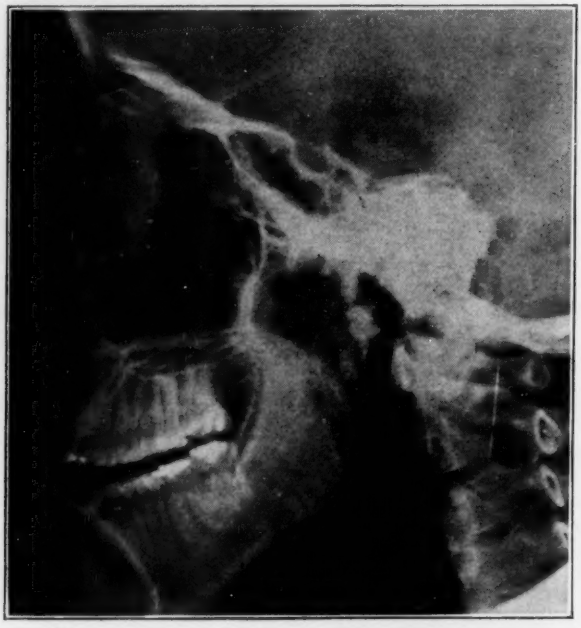

Fig. 2.—Roentgenogram showing the recurrent tumor with its tooth.

The pathologic diagnosis was: benign osteofibroma (dentigerous origin—tooth in malposition).

Progress.—March 23, 1934: The nasopharynx showed normal resolution. There was still some slight crusting in the lateral pharyngeal space but no evidence of tumor. The orifice of the eustachian tube could not be made out.

April 10: The lateral wall of the nasopharynx was healed. No granulation was seen.

May 24: There was moderate enlargement of the lymphoid tissue on the left lateral wall of the nasopharynx but no bony growth.

April 15, 1935: The lateral wall of the nasopharynx was smooth and clean. It was still not possible to make out any orifice of the eustachian tube. The patient still complained of "about the same deafness" in the left ear.

March 13, 1942: The patient complained of pain in the left ear with fulness. There was suggestive recurrence on the left lateral wall, the lesion being about

the size of a lima bean. It appeared to be situated more mesially and was slightly more movable. There was no inflammatory reaction and no pain on palpation. At this time there was definite acute myringitis of the left ear, which responded to conservative treatment.

March 30: Stereoscopic left lateral and submentovertix roentgen projections of the skull revealed a dense shadow resembling a dental structure lying in the posterior wall of the pharynx, on the left side, in the region of the orifice of the eustachian tube. Surrounding this shadow was a larger shadow of lesser density which appeared to be calcification with a cyst wall.

The conclusion was that a dermoid cyst was lying in the posterior wall of the nasopharynx, on the left side.

Second Surgical Procedure and Observations.—On May 27, 1942, with the patient under general anesthesia, the recurring tumor with the deciduous tooth was removed through the route used in the previous operation.

A firm fibrocartilaginous tumor of the left lateral nasal wall, above the soft palate, was found, which appeared to be free in the cavity of the previous operation

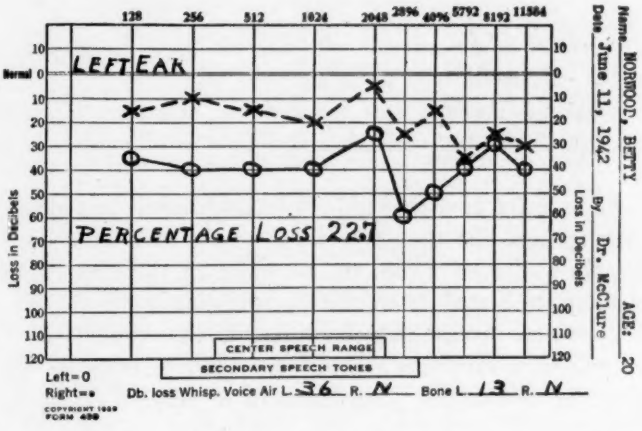

Fig. 3.—Audiogram taken June 11, 1942 showing rather typical conductive deafness of the left ear. The right ear is normal. Air conduction o—o; bone conduction x— —x.

but firmly fixed in its lateral aspect. A deciduous tooth was removed from the posterior portion, firmly attached to bony tissue of the tumor. The base of the tumor consisted of cancellous bone. It appeared to have some posterior attachment at the angle of the mandible. No bleeding was encountered, and no packing or sutures were necessary.

Pathologic Report.—Gross Description: The specimen was nine irregularly shaped pieces of tissue and a small molar tooth. The pieces of tissue varied from 0.5 to 2 cm. in length to a dome 2 cm. wide and about 0.75 cm high. This dome and two other pieces of tissue measuring about 1.5 by 0.5 by 0.5 cm. had pearly gray surfaces, and the cut surfaces revealed extremely firm, gritty, white, dense tissue. There were two small fragments of bone, and three of the fragments had granular reddish surfaces over part of these. One of the three larger pieces of tissue on section was composed of a softer, pale yellow tissue.

Microscopic Description: The sections were partly covered by squamous epithelium, which in some sections was hyperplastic and dipped deeply into the underlying stroma. The basal layer was cuboidal and never resembled the very tall columnar epithelium of the adamantoblast. In one section there was an ulcerated surface with many dilated capillaries and a heavy infiltration of lymphocytes and plasma cells at the base of the ulcer. The bulk of the interior of the tissue was dense hyalinized material almost devoid of nuclei. In some sections there were mucous glands and one small atypical piece of cartilage. The mucous glands were probably from the adjacent oral mucosa. The dense hyalinized matrix, covered by squamous epithelium, closely resembled the sections from the previously excised tumor. Although this tumor recurred, it continued to appear histologically benign and inert.

The pathologic diagnosis was odontoma.

Progress Note, June 11, 1942.—"The nasopharynx is smooth and clean, with no evidence of recurrence of the growth. The patient was discharged with instructions to have occasional observation of the pharynx. An audiogram made on this date reveals rather typical conductive deafness of the left ear. The right ear is normal."

SUMMARY OF CASE AND COMMENT

The character of the growth with the deciduous tooth puts it in the classification of osteofibroma of dentigerous origin.

The location is unusual, rare for this type of tumor. Careful search of the literature does not reveal a single case of odontoma of the nasopharynx.

The origin of the growth could not be determined, but apparently the tumor sprang from the posterior ramus of the mandible. A tumor of this type when situated within the mandible or the maxilla appears to be completely separated from the surrounding bone by its capsule; therefore, one may assume that this tumor had no attachment.

The audiogram reveals a typical conductive hearing loss in the left ear, due either to complete obstruction or to absence of the eustachian tube.

The recurrence of the tumor was definitely due to a small portion of the capsule in the extreme lateral part remaining, which contained tooth remnants in the bony structure, with the power of regrowth. This regrowth is typical of odontoma, with the second tooth presenting itself to the surface—in this case, the nasopharynx.

The recurrence of growth and the formation of a second deciduous tooth definitely put the tumor in the classification of compound composite odontoma.

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EFFECT OF LABYRINTHINE REFLEXES ON THE VEGETATIVE NERVOUS SYSTEM

A Review

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THE second World War has revived the interest in seasickness and airsickness. The chief signs and symptoms of these syndromes are vegetative disturbances such as vasomotor reactions, pallor of the face, perspiration, nausea and vomiting (Byrne [1]). Although it is recognized that seasickness is due chiefly to abnormal excitation of the labyrinth (Kreidl [2] and James [3]) and a similar assumption is rather probable for airsickness (Armstrong [4]), symptomatologic clinical studies alone are insufficient in order to decide whether the aforementioned vegetative symptoms are secondary effects of vertigo and the associated emotional corticodiencephalic reactions or whether they are the direct reflex effect of excitation of the nonacoustic inner ear. Experiments on animals are able to demonstrate the reflex nature of the majority of these vegetative reactions.

VASOMOTOR REACTIONS

The certain evidence that stimulation of the labyrinth leads to a vasomotor reaction is furnished by experiments in which the blood pressure in rabbits was recorded during as well as after rotation (Spiegel and Démétriades [5]). These experiments showed that a fall of blood pressure develops in some cases during rotation and in others after rotation has ceased. The depressor reaction may be preceded by a slight rise and may also be followed by a pressor reaction, so that often a multiphase reaction presents itself. Similar reactions were observed

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1. Byrne, J.: Physiology of the Semicircular Canals and Their Relation to Seasickness, New York, J. T. Dougherty, 1912.

2. (*a*) Kreidl, A.: Ergebn. d. Physiol. **5**:572, 1906. (*b*) Kreidl, A., cited by Ewald and Wollenberg, in Hitzig: Der Schwindel, in Nothnagel, C. W. H.: Handbuch der speziellen Pathologie, Vienna, A. Hölder, 1911, vol. 12.

3. James W.: Am. J. Otol. **4**:239, 1882.

4. Armstrong, H. G.: Principles and Practice of Aviation Medicine, Baltimore, Williams & Wilkins Company, 1939.

5. Spiegel, E. A., and Démétriades, T.: Arch. f. d. ges. Physiol. **196**: 185, 1922.

in cats, dogs and guinea pigs on rotation around the longitudinal axis of the body as well as on rotation around a dorsoventral axis. They occur independently of gastrointestinal reactions.

Vasodepressor reactions could also be observed in rabbits on mechanical stimulation of the eighth nerve and on caloric and galvanic stimulation of the labyrinth (Spiegel and Démétriades [5]) and in dogs on caloric stimulation (Kremer [6]), in the latter case, however, without proving the vestibular origin of the reaction. This depression sets in early, a few seconds after the beginning of the stimulation, but the return of the blood pressure to its former level is much more gradual, the depression thus lasting for rather a long time, up to fifty seconds. Sometimes the depression is followed by a slight increase of pressure, the ascending limb of the curve exceeding the original level, before the curve returns to the original level. The nystagmus and the fall of blood pressure do not as a rule strictly coincide; the nystagmus may outlast the depression of blood pressure but may also end earlier. The part played by the labyrinth in this lowering of the blood pressure is shown by the fact that the reaction can be elicited after intracranial transection of the trigeminal nerve or of the glossopharyngeal-vagus roots; but, after intracranial transection of the eighth nerve, caloric stimulation on the side of the operation fails to evoke this reaction (Spiegel and Démétriades [5]).

The observation that the various types of stimulation of the labyrinth (rotatory, galvanic and caloric) induce fall of blood pressure has been repeatedly confirmed (Pupilli,[7] Hasama,[8] Cantele [9] and Mark and Seifert [10]). The type of anesthetic used seems to have an influence on the reaction. While the fall of blood pressure was observed in rabbits under anesthesia induced with ether and ethyl carbamate, a rise of blood pressure may occur in morphinized rabbits (Mies [11]). In interpreting these observations (Démétriades and Spiegel [12]), one has to bear in mind that morphine may change the excitability of the vegetative system, e. g., it decreases the vagotonic oculocardiac reaction and increases the sympathicotonic solar phenomenon (Claude, Tinel and Santenoise [13]).

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6. Kremer, J. H.: DeZeeziekte, Thesis, Amsterdam, 1921.
7. Pupilli, G: Arch. ital. de biol. **77**:195, 1926.
8. Hasama, B.: Arch. internat. de pharmacodyn. et de thérap. **40**:204, 1931.
9. Cantele, P.: Arch. ital. di otol. **44**:129, 1933.
10. Mark, R. E., and Seifert, L. B.: Ztschr. f. d. ges. exper. Med. **93**:685, 1934.
11. Mies, H.: Ztschr. f. Biol. **97**:218, 1936.
12. Démétriades, T., and Spiegel, E.: Ztschr. f. Biol. **98**:151, 1937.
13. Claude, H.; Tinel, J., and Santenoise, D.: Compt. rend. Soc. de biol. **87**:1347, 1922.

In view of these experiences, the reactions of unanesthetized animals are of interest. In decerebrate rabbits Spiegel and Démétriades [14] observed the vasodepressor effect on labyrinthine stimulation. In curarized cats rotation produced irregular responses, mainly pressor reactions, while in decerebrate cats rotation induced a fall of blood pressure, similar to that in cats under anesthesia induced with pentobarbital sodium.[15] Thus, in unanesthetized animals, pressor impulses from the prosencephalon and the diencephalon may be superimposed on and mask the labyrinthine vasodepressor reflex.

PERIPHERAL RECEPTOR APPARATUS

After both labyrinths had been paralyzed by local injection of a 20 per cent cocaine solution (Spiegel and Démétriades [5]), there was absence of nystagmus after turning and after caloric stimulation as well as absence of the vasodepressor reaction on calorization, while strong galvanic stimulation (20 to 25 milliamperes) acting on the trunk of the eighth nerve still had an effect. When the cocaine had paralyzed the labyrinths, turning of the animals failed to evoke the previously well marked depression of blood pressure, or this effect was at least distinctly weakened. In other cases it was even observed that the slight rise of pressure that sometimes appears at the beginning of the turning increased as the labyrinth became paralyzed. This last experience may perhaps indicate that the depressive effect may be superimposed on pressor reflexes that are at least partly actuated by stimulation of other sensory nerves on rotation.

The action of the labyrinth on the blood pressure has therefore been compared with that of the depressor nerve of the vagus (Spiegel and Démétriades [5]). The reflex action of the latter nerve tends to compensate for the rise of intra-aortic pressure; it has been suggested as a working hypothesis that the vestibular nerve acts in a similar way, namely, that it tends to compensate for increases of pressure caused by stimulation of other sensory nerves on brisk movements of the head.

Following bilateral puncture of the round windows in cats, rotation may fail to produce rhythmic ocular movements while a reflex depression of blood pressure can still be elicited by rotation of the body around a longitudinal or around a dorsoventral axis (Spiegel, Oppenheimer and Wycis [16]). Subsequent injection of a 2 per cent alcoholic cocaine solution into both labyrinths transitorily abolished the vasomotor reaction, indicating, in agreement with previous experiments, that the

14. Spiegel, E. A., and Démétriades, T.: Arch. f. d. ges. Physiol. **205**: 328, 1924.

15. Oppenheimer, M. J., and Spiegel, E. A.: To be published.

16. Spiegel, E. A.; Oppenheimer, M. J., and Wycis, H. T.: Federation Proc. **3**:44, 1944.

receptor apparatus lies in the labyrinth. In a second group of experiments, guinea pigs were subjected to centrifugation (method of Wittmaack, Magnus and de Kleyn), so that histologic examination revealed that the otoliths were detached from all the maculas (Lindsay, Oppenheimer, Wycis and Spiegel [17]). After this centrifugation, the animals were tested during the stage in which the tonic labyrinthine reactions were paralyzed. In this stage rotation still produced a fall in blood pressure. Thus, paralysis of the receptors for labyrinthine kinetic reactions such as the rhythmic eye jerks or of the receptors for tonic labyrinthine reflexes does not prevent the vasomotor reaction to rotation, while paralysis of the labyrinth induced with cocaine abolishes this reaction. These experiments seem to indicate that the receptor apparatus of the vasomotor reaction cannot be localized in sharply restricted parts of the labyrinth and that stimulation of the maculas as well as of the cristae may be able to elicit this reaction, particularly on fast rotation.

The threshold values of the vasomotor reaction to rotation lie higher than those of the ocular reaction [18]; thus, if the threshold of the former reaction is not reached (Arslan [19]), rotation may elicit nystagmus without changes in the systemic blood pressure. Ampullopetal flow of the endolymph in the horizontal canals has a more pronounced vasodepressor effect than ampullofugal flow (Hasama [8]).

Central Mechanism.—The vestibular depression of blood pressure was retained after transection of the midbrain, but after destruction of the nucleus triangularis it could no longer be elicited by caloric stimulation on the side of the operation (Spiegel and Démétriades [14]). Apparently the vestibular impulses are transmitted chiefly through the nucleus triangularis to the vasomotor center in the substantia reticularis. (For theoretic considerations of the function of the various parts of the vestibular nuclei see Marburg [20] and Spitzer.[21])

Effector Mechanism.—An inhibition of the heart through stimulation of the vagus nerve as well as a dilatation of the vessels of the head seems to be of little or no significance, since bilateral vagotomy and also bilateral section of the cervical sympathetic trunk leave the reflex almost unaltered. Transection of the spinal cord above the origin of the splanchnic nerve (at the junction of the cervical and thoracic parts of the spinal cord) does, however, cause almost a disappearance of the

17. Lindsay, J. R.; Oppenheimer, M. J.; Wycis, H. T., and Spiegel, E. A.: The Receptor Apparatus of Vestibulo-Vasomotor Reactions, Arch. Otolaryng. **42**:257 (Oct.) 1945.

18. Spiegel, E. A.: Unpublished experiments.

19. Arslan, K.: Riv. di clin. med. **1**: 1, 1940.

20. Alexander, G., and Marburg, O.: Handbuch der Neurologie des Ohres, Berlin, Urban & Schwarzenberg, 1923, vol. 1, p. 175.

21. Spitzer, A.: Arb. a. d. neurol. Inst. a. d. Wien. Univ. **25**:423, 1924.

depression; only in a few of the experiments was a slight depression retained (Spiegel and Démétriades [5]). In further experiments, the flow of blood from the rest of the body into the abdominal viscera following splanchnicotomy was prevented by the preliminary step of tying the abdominal aorta just below the diaphragm as well as by tying the vena cava and the portal veins, so that blood could get into the splanchnic area by a back flow only through the hepatic veins. In this way the pressure was maintained at the old level in spite of section of the splanchnic nerves. In such preparations, lowering of the blood pressure could still be observed on stimulation of the labyrinth even after bilateral splanchnicotomy (Spiegel and Démétriades [5]). It seems, therefore, that we are dealing here with mechanisms similar to those involved in the reflex action of the depressor vagi (Bayliss [22] and Asher [23]) nerves: the depression is due only partly to relaxation of the vasconstrictor nerves in the splanchnic area and partly to reaction of other vascular areas. In fact, plethysmographic studies revealed also vascular reactions in the limbs (see later) on labyrinthine stimulation.

The vestibular depression of blood pressure does not leave the cerebral circulation unaffected. Parallel changes in the cerebral plethysmogram and the cerebrospinal fluid pressure have been observed on caloric stimulation of the labyrinths in rabbits (Spiegel and Démétriades [14]). By means of a thermocouple inserted into the parietal lobes of cats (Gibbs-Schmidt's method), a slowing of the cerebral circulation was observed on caloric and galvanic stimulation of the labyrinth as well as on rotation (Spiegel, Henny and Wycis [24]). This change was still demonstrable after combined extirpation of the vasoconstrictor pathway (cervical sympathetic trunk) and of the vasodilator pathway to the cerebrum (facial–great superficial petrosal nerve). It is apparently chiefly a passive change induced by the fall of systemic blood pressure.

VASOMOTOR REACTIONS IN HUMAN BEINGS

The depressive vasomotor effect of caloric and rotational stimulation of the labyrinth may in a group of cases (type 1 of Wotzilka [25]) be complicated by an initial rise of blood pressure. The usual phenomenon in all of Wotzilka's cases was, however, a fall of blood pressure (uncomplicated by the initial rise in type 2). Similar observations have been made by others (Talpis and Wolfskowitsch,[26] Cantele and Scarpa [27] and

22. Bayliss, W. M.: J. Physiol. **28**:276, 1902.
23. Asher, L.: Ztschr. f. Biol. **52**:298, 1908; **68**:160, 1918.
24. Spiegel, E. A.; Henny, G. C., and Wycis, H. T.: Am. J. Physiol. **142**: 589, 1944.
25. Wotzilka, G.: Ztschr. f. Hals-, Nasen- u. Ohrenh. **10**:127, 1924; **12**: 649, 1925.
26. Talpis, L., and Wolfskowitsch, M.: Monatschr. f. Ohrenh. **62**:1278, 1928.
27. Cantele, P. G., and Scarpa, A.: Arch. ital. di otol. **45**:884, 1934.

Rosselli del Turco [28]). The initial rise had already been observed in some of the aforementioned experiments on rabbits; as already pointed out, this phenomenon may be increased after labyrinthectomy (Spiegel and Démétriades [5]). In experiments on unanesthetized persons, one must bear in mind the effects of emotions associated with or induced by vertigo. The mere proposition that an examination of the labyrinth is to be repeated may be sufficient to raise the patient's blood pressure (Stein and Bénesi [29]). On thermic stimulation of the labyrinth, plethysmographic studies revealed a vasodilator reaction in the arm; an occasional vasoconstriction under the same conditions has been interpreted as due to psychic reactions (de Crinis and Unterberger [30]). A brief vasoconstriction preceding the vasodilatation in the limbs on caloric (Maestranzi [31]) or galvanic (Rosselli del Turco [28]) stimulation of the ear has been interpreted as due to stimulation of sensory nerves in the external auditory canal. In agreement with such an interpretation, thermic stimulation on the side of an unexcitable labyrinth produced vasconstriction only (Roselli del Turco [28]). The results of capillaroscopic studies [32] hardly permit definite conclusions.

On caloric stimulation, the pressure in the retinal arteries shows a biphasic reaction: an initial rise may be followed by a prolonged fall (Worms and Chams [33]), or the pressure first falls and then rises (Streiff, Montandon and Monnier [34]); similar changes in the cerebral arteries may be suspected, and the state of filling of the retinal veins decreases (Démétriades [35]). In seasickness it has been observed (Kramer [36]) that the retinal vessels have a small diameter; the choroid may show a paleness comparable to that found in persons suffering from chronic hemorrhage.

CARDIAC NERVES

There are essentially no changes in the electrocardiograms of rabbits and cats under anesthesia induced by ethyl carbamate during and after

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28. Rosselli del Turco, L.: Rassegna di neurol. veget. **1**:211, 1938.

29. Stein, C., and Bénesi, O.: Monatschr. f. Ohrenh. **58**:581, 1924.

30. de Crinis, M., and Unterberger, S.: Ztschr. f. Hals-, Nasen- u. Ohrenh. **24**:504, 1929.

31. Maestranzi, D.: Ann. di laring., otol. **2**:129, 1926.

32. Zanni, G.: Valsalva **3**:245, 1927. Marinesco, G.; Draganesco, S.: Kreindler, A., and Bruch, A.: Compt. rend. Soc. de biol. **106**:103, 1930. Patroni, A.: Valsalva **11**:708, 1935. Scevola, P., and Ventura Gregorini, F.: Arch. ital. di otol. **50**:393, 1938.

33. Worms, G., and Chams, G.: Rev. d'otol. **9**:595, 1931; Bull. Soc. franç. d'opht., 1931, p. 525.

34. Streiff, E. B.; Montandon, A., and Monnier, M.: Confinia neurol. **4**: 347, 1942.

35. Démétriades, T.: Personal communication to the author.

36. Kramer, L.: Prag. med. Wchnschr. **17**:465 and 477, 1892.

rotation (Spiegel [37]). In dogs under morphine anesthesia, there were signs of an excitation of the accelerator nerves; these changes were, however, absent after decerebration by transection of the midbrain and therefore are to be regarded as secondary and induced by emotion. Thus, in these experiments on mammals, a reflex influence of the labyrinth on the heart was not demonstrable. Also in human beings the present material (Maestranzi,[31] Ciurlo,[38] Pick [39] and Della Torre and Cantele [40]) does not permit definite conclusions regarding the existence of vestibular reflexes on the vagal fibers to the heart. Experiments with caloric or galvanic stimulation are hardly of value for answering this problem, because simple mechanical stimulation of the external auditory meatus is sufficient to elicit bradycardia (Scheminsky [41]). After rotation slight slowing of the pulse may be observed in some instances; in most persons there is slight tachycardia, which probably is an emotional reaction as indicated by the aforementioned experiments on animals. In human beings the effect of labyrinthine stimulation on the oculocardiac reflex has also been studied (Kotyza [42]). Rotation increased the tonus of the parasympathetic system more than that of the sympathetic system; caloric stimulation, however, decreased the "vegetative tonus." On encroachment of an inflammation of the middle ear on the labyrinth, bradycardia has been observed; this effect has been interpreted as a reflex action of the labyrinth on the cardiac nerves (Borries [43] and Neumann [44]). Since the lymphatic spaces of the labyrinth are in communication with the subarachnoid space and hence a collateral inflammation in the posterior fossa may readily occur, the possibility should be borne in mind that the bradycardia observed in labyrinthitis may be a sign of a direct irritation of the vagal roots. Transient bradycardia in the initial stage of a hemorrhage that followed a radical operation for suppuration of the middle ear (Beck [45]) also does not permit conclusions, since there is no proof that the reflex stimuli originated in the labyrinth.

GASTROINTESTINAL REACTIONS

The changes in tonus and motility of the stomach when nausea and vomiting are induced by labyrinthine stimulation are principally similar

37. Spiegel, E. A., in Alexander and Marburg,[20] 1928, vol. 3, p. 631.
38. Ciurlo, L., and Santucci, G.: Arch. ital. di otol. **45**:353, 1934.
39. Pick, E.: Arch. ital. di otol. **45**:720, 1934.
40. Della Torre, G., and Cantele, P. G.: Riv. oto-neuro-oftal. **14**:1, 1937.
41. Scheminsky, F.: Arch. f. d. ges. Physiol. **194**:527, 1922.
42. Kotyza, F.: Acta oto-laryng. **25**:51, 1937.
43. Borries, G. V., in Proceedings of the Danish Otolaryngological Society, Copenhagen, April 4, 1923; Monatschr. f. Ohrenh. **61**:205, 1927.
44. Neumann, H.: Monatschr. f. Ohrenh. **58**:177 and 190, 1924.
45. Beck, J.: Ztschr. f. Hals-, Nasen- u. Ohrenh. **27**:586, 1930.

(Byrne [1] and Lebensohn [46]) to those observed when these conditions are caused by other reflex stimuli. Nausea is associated with relaxation of the fundus of the stomach, cessation of the antral waves (Keeton and Nelson [47]), closure of the pylorus and duodenal antiperistalsis (Brunemeier and Carlson,[48] Alvarez [49] and Ivy, Vloedman and Keane [50]). In vomiting the changes progress; there is not only closure of the pylorus (splanchnic impulses) but also contraction of the pyloric part of the stomach, relaxation of the fundus, inhibition of the cardia [51] and esophagus (chiefly vagal impulses), closure of the glottis with inhibition of respiration, stimulation and inhibition of the diaphragm and contraction of the abdominal muscles (Cannon [52] and Hatcher [53]). As a part of the nausea complex on caloric labyrinthine stimulation in human beings, contraction of the descending duodenum has been observed; it tends to expel the duodenal contents into the stomach (Ingelfinger [54]). According to these observations, absolute pylorospasm during nausea would be impossible.

On caloric or galvanic stimulation of the ear, the reflex effect from the labyrinth may be preceded or complicated by reflexes from sensory nerves of the external ear (e. g., initial rise in gastric tone [Lebensohn [46]]). Emotional influences may be an additional factor (Lunedei [55]). It seems, for instance, questionable whether the hypoacidity and mucosal pallor observed in a patient with gastric fistula on labyrinthine stimulation (Wolf and Wolff [56]) were true reflex effects or emotional reactions.

It seems that loss of the vagal impulses disturbs vomiting on labyrinthine stimulation for some time only. This is indicated by the observation that animals in which the vagus has been cut might still become seasick (Kreidl [2b]).

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46. Lebensohn, J. E.: Car-Sickness, Arch. Ophth. **4**:342 (Sept.) 1930.

47. Keeton, R. W., and Nelson, E. S.: Treatment of Nausea and Certain Related Circulatory Sensation, J. A. M. A. **90**:683 (March 3) 1928.

48. Brunemeier, E. H., and Carlson, A. J.: Am. J. Physiol. **36**:191, 1915.

49. Alvarez, W. C.: Reverse Peristalsis in Bowel, Precursor of Vomiting, J. A. M. A. **85**:1051 (Oct. 3) 1925.

50. Ivy, A. C.; Vloedman, D., and Keane, J.: Am. J. Physiol. **72**:99, 1925.

51. However, in the dog an inhibition of the cardia on galvanic or caloric stimulation of the ear could not be found (Ventura Gregorini, F.: Arch. ital. di otol. **51**:1, 1939).

52. Cannon, W. B.: Am. J. Physiol. **1**:359, 1898.

53. Hatcher, R. A.: Physiol. Rev. **4**:479, 1924.

54. Ingelfinger, F. J., and Moss, R. E.: Am. J. Physiol. **136**:561, 1942.

55. Lunedei, A.: Riv. di clin. med. **29**:1017 and 1043, 1928.

56. Wolf, S., and Wolff, H. G.: Human Gastric Function, London, Oxford University Press, 1943.

57. Footnote deleted by author.

The reflex action of the labyrinth on the small intestine has been studied in rabbits (Spiegel and Démétriades [58]). Caloric stimulation of the labyrinth induced an increase of the pendular movements of the small intestine and of its tonus. Here two components were involved—a short-lasting reaction, elicited from the sensory nerve endings of the external and the middle ear, and a long-lasting reaction, of vestibular origin, following the former immediately or after a latent period of some seconds. This reaction was retained after transection of the midbrain and was brought about by reflex stimulation of both vagal nerves (Spiegel and Démétriades [58]). After elimination of the labyrinths, a transitory reduction of the motility of the stomach and intestine was found (Le Heux and de Kleyn [59]).

The reflex action on the cranial autonomic nervous system is not limited to the intestinal vagus; it affects also the nerves that supply the salivary glands, i. e., centrifugal vegetative fibers joining the seventh and ninth cranial nerves. On excitation of the labyrinth increased secretion of saliva was found in dogs (Kremer [6]); this indicates a reflex influence on the bulbar nuclei of the nerves of the salivary glands. These experiments were, however, limited to caloric stimulation, and the observed increase of the salivary secretion may partly be referred to the excitation of nerves to the salivary glands that course through the middle ear (chorda tympani and tympanic nerve). It seems, therefore, important that rotation may also elicit pronounced salivation in susceptible dogs.[60]

RESPIRATORY REACTION.

Tonic labyrinthine reflexes on the respiration were observed in ducks (Huxley [61] and Paton [62]). Supine position inhibits the respiration in decerebrate animals, while extirpation of the labyrinths abolishes this reaction. Linear accelerated movements (progressive movements) produced in frogs first a rise of the intrapulmonary pressure and then an absence of pulmonary movements. In this second stage the larynx remains closed; however, the intrapulmonary pressure shows fluctuations that have been interpreted as due to contractions of the walls of the lungs (Brown [63]).

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58. Spiegel, E., and Démétriades, T.: Monatschr. f. Ohrenh. **58**:63, 1924.

59. Le Heux, J., and de Kleyn, A.: Verhandel. d. k. Akad. v. Wetensch. **34**: 836, 1931; Acta oto-laryng. **17**:158, 1932.

60. Spiegel, E. A.: Unpublished observations.

61. Huxley, F. M.: J. Physiol. **44**:24 P, 1912; Quart. J. Exper. Physiol. **6**: 159, 1913.

62. Paton, N.: Quart. J. Exper. Physiol. **6**:197, 1913; in Proceedings of the Eleventh International Physiological Congress, Edinburgh, 1923.

63. Brown, G. T.: Arch. f. d. ges. Physiol. **130**:193, 1909.

Rhythmic linear vertical movements (Sjöberg [64]) and rhythmic pitching movements (Spiegel [65]) induce an increase in the frequency and amplitude of respiration in cats and dogs. These effects persist after extirpation of the cerebral hemispheres, the thalamus and the hypothalamus (Spiegel [65]). Thus the respiratory reactions to vertical movements are at least partly due to brain stem reflexes. If the activity of the respiratory center was depressed, an inhibitory reaction sometimes appeared. An analysis of the part played by the various receptors showed, on the basis of extirpation experiments, that impulses mainly from the labyrinth and from the spinal nerves participate in producing the respiratory reactions to vertical movements while retinal impulses play a subsidiary part only. These respiratory reactions appear independently of the reaction of the vasomotor and digestive apparatus.

A study of the effect of caloric stimulation of the ear on the bronchi in rabbits, dogs and cats showed only in some instances a slight contraction (Spiegel [37]).

During cold irrigation of the ear in human beings, the respiratory curve shows no regular alteration in the length of inspiration and expiration. The ratio of inspiration to expiration ("respiratory relation") is increased as a rule, owing to relative prolongation of inspiration (Allers and Leidler [66]). During the appearance of nystagmus a typical alteration of the respiratory curve, of variable duration, has been found, namely, shortening of inspiration and prolongation of expiration. Eventually there may be a respiratory pause, lasting several seconds. The respiratory relation is almost always appreciably diminished (Allers and Leidler [66]). The intensity of this reaction is independent of the intensity of the nystagmus and of the presence or absence of vertigo. It is not observed in optic nystagmus; hence it has been considered as due to labyrinthine inhibition of the central mechanism of inspiration (Allers and Leidler [66]). It may perhaps be related to the inhibition of the respiratory center in vomiting.

PUPILLARY REACTIONS

Dilatation of the pupils was observed on thermic stimulation of the labyrinth (Udvarhelyi [67]), on production of increased pressure in the external auditory canal (Urbantschitsch [68]) and on galvanization of the head (Eulenburg and Schmidt [69]). In the appraisal of these observa-

64. Sjöberg, A. A.: Acta oto-laryng., 1931, supp. 14, p. 1.
65. Spiegel, E. A.: Am. J. Physiol. **117**:349, 1936.
66. Allers, R., and Leidler, R.: Arch. f. d. ges. Physiol. **202**:278, 1923.
67. Udvarhelyi, K.: Ztschr. f. Ohrenh. **67**:136, 1913.
68. Urbantschitsch, V.: Wien. klin. Wchnschr. **9**:1, 1896.
69. Eulenburg and Schmidt: Zentralbl. f. d. med. Wissensch., 1868, p. 321.

tions two possibilities should be borne in mind. First, pupillodilator reflexes may be elicited by stimulation of the sensory nerve endings in the external auditory canal; second, not only in animals (de Kleyn and Socin [70]), but also in human beings (Siebenmann [71] and Spiegel [72]) the postganglionic fibers coursing to the dilator of the pupil from the superior cervical ganglion apparently come into relationship with the medial wall of the tympanic cavity and hence may be affected by caloric or galvanic stimulation of the ear.

Therefore, only rotation is appropriate for the study of vestibular pupillary reactions (Wodak and Fischer [73] and Spiegel [74]). During the turning, the vestibular stimuli induce a gradually increasing constriction; after the turning has ended, the miosis suddenly becomes well pronounced, giving way to mydriasis followed by hippus. This could be observed by entoptic subjective observations (Wodak and Fischer [73]) as well as by means of an apparatus permitting an investigator standing in front of the turning chair to observe the pupil of a human or animal subject during all stages of the turning (Spiegel [74]). The pupillary changes are brought about through transmission of labyrinthine reflex impulses to the oculomotor nerves, chiefly by way of the medial longitudinal fasciculus, each labyrinth influencing the centers of the sphincter pupillae muscle on both sides. In the production of the hippus not only vestibular reflex impulses but also other factors (psychic excitation) seem to play a part (Spiegel [74]). Integrity of the cervical sympathetic nerve is not necessary for this reaction, as was shown by experiments on animals and observations on patients with Horner's syndrome (Spiegel [74]). It is interesting that in patients with Argyll-Robertson pupils there is in the majority of cases a "dissociated disturbance of the vestibular reflexes to the eye"—an extinction of the vestibular pupillary reaction, with preservation of the reflexes on the external muscles of the eye (Spiegel [75]).

OTHER ORGANS

Stimulation of the labyrinth by calorization or rotation may induce in rabbits increase of the tone of the uterus and of the frequency of its contractions (Concetti and Masera [76]). However, it has not been excluded that one is dealing with the effects of excitation of cortico-

70. de Kleyn, A., and Socin, C.: Arch. f. d. ges. Physiol. **160**:407, 1915.

71. Siebenmann, F., cited by Metzner, R., and Wölfflin, E.: Arch. f. Ophth. **89**:308, 1915.

72. Spiegel, E. A., in Alexander and Marburg,[20] 1928, vol. 2, p. 77.

73. Wodak, E., and Fischer, M. H.: Beitr. z. Anat., Physiol., Path. u. Therap. d. Ohres **19**:15, 1923.

74. Spiegel, E. A.: Arb. a. d. neurol. Inst. a. d. Wien. Univ. **25**:413, 1924.

75. Spiegel, E. A.: Wien. klin. Wchnschr. **38**:189 and 216, 1925.

76. Concetti, E., and Masera, R., cited by Arslan.[19]

diencephalic centers. The same statement applied to the changes in the blood sugar level (Gatteschi[77] and Gatteschi and Rodolfo-Masera[78]) and to the increase in the negative potential of the adrenals and in the discharge of epinephrine into the blood stream (Hasama[79]) observed after such stimulation.

CONCLUDING COMMENT

An analysis of the signs and symptoms associated with labyrinthine stimulation has to differentiate between cortical and diencephalic reactions (disturbances of orientation and emotional reactions), on the one hand, and simple reflex effects of labyrinthine origin, on the other hand. For a number of vegetative reactions to labyrinthine stimulation, such as some vasomotor, intestinal and respiratory reactions, it has been shown that they are rhombencephalic reflexes and that the higher parts of the central nervous system are dispensable. However, corticodiencephalic impulses may modify these reactions. On the other hand, these rhombencephalic reflexes may influence the state of the higher centers; this is indicated by the changes in cerebral circulation that depend chiefly on the changes in systemic blood pressure associated with labyrinthine stimulation. Since impairment or fluctuation of the cerebral circulation may give rise to sensations akin to vertigo, such indirect effects of labyrinthine vegetative reflexes on the cerebrum may play a part in the mechanism of labyrinthine vertigo besides the disturbances of orientation.

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77. Gatteschi, G.: Arch. ital. di otol. **50**:243, 1938.
78. Gatteschi, G., and Rodolfo-Masera, T.: Arch. ital. di otol. **51**:105, 1939.
79. Hasama, B.: Arch. f. d. ges. Physiol. **239**:680, 1937.

Progress in Otolaryngology

Summaries of the Bibliographic Material Available in the Field of Otolaryngology

ADVANCES IN THE UNDERSTANDING OF RHINOLOGIC AND OTOLOGIC CONDITIONS RELATED TO THE NERVOUS SYSTEM

A Critical Survey of the Literature

WELLS P. EAGLETON, M.D., Sc.D.
NEWARK, N. J.

(Concluded from Page 662)

ABSCESS OF THE BRAIN

Bacteriologic Findings.

McFarlan [243] reports the results of bacteriologic studies of 48 cases of abscess of the brain.

Site of Abscess.—Forty-two patients had a single abscess; 6 had more than one. Of those with a single abscess, 3 had a cerebellar abscess, 18 an abscess of the frontal lobe, 5 one of the parietal lobe, 15 one of the temporal lobe, and 1 had an abscess of the occipital lobe.

Probable Source of Infection.—Disease of the ear was the source of infection in 18 patients, sinusitis in 7, infection of the lungs in 7, trauma (penetrating injury) in 3, staphylococcic septicemia in 1, subacute bacterial endocarditis in 1 and puerperal sepsis in 1. In 4 patients the source of the infection of the brain was unknown.

Duration of Symptoms.—The duration of the symptoms of abscess was known in 47 cases; in 15 it was less than one month at the time the patient was hospitalized; in 22 it was between one and three months, in 6 between four and seven months, and in 4 a year or more.

Commonest Organism in Abscess of the Brain.—"Analysis of the bacteriologic findings . . . revealed no close association between the type of organism and the site of abscess or source of infection. . . . Rapidly fatal cases which do not reach the neurosurgeon might give different results."

Although Staphylococcus aureus was present in 15 of the 48 cases in this series and in 14 of 27 cases reported by Alpers [244] (1939),

243. McFarlan, A. M.: The Bacteriology of Brain Abscess, Brit. M. J. **2**: 643-644 (Nov. 20) 1943.

244. Alpers, B. J.: Abscess of Brain; Relation of Histologic to Clinical Features, Arch. Otolaryng. **29**:199-222 (Feb.) 1939.

other authors found this organism in only a few of their cases of abscess of the brain. In infants staphylococci are said to be very common (Sanford,[245] 1928). Fusiform bacilli and anaerobic streptococci each occurred in 10 cases. On several occasions pneumococci grew only anaerobically in primary cultures. Streptococcus pneumoniae, Proteus vulgaris and Streptococcus pyogenes were also observed in several cases.

Encapsulation.—Clinical evidence of encapsulation was obtained in 5 cases two months and in 8 cases three months after the onset of symptoms. Histologic examination showed well marked fibrous walls in 2 (pneumococcic) cases with six weeks' history, in 3 cases with two months' and in 6 cases with three months' history. A deeper unencapsulated loculus occurred in several abscesses, which had apparently been present for six months or longer. It was therefore impossible to draw any general conclusion about the time relations of capsule formation or to compare abscesses due to different organisms with regard to speed of encapsulation.

There are both clinical and experimental data indicating that encapsulation occurs in the presence of fusiform bacilli or anaerobic streptococci. Well formed capsules were found in 2 abscesses in which P. vulgaris was present.

Summary.—"Specimens of pus from 48 brain abscesses were examined, . . . 33 yielded a single organism and 14 more than one species of organism. One specimen was sterile.

"Anaerobic culture is a necessary part of the examination of pus from brain abscesses both for the isolation of . . . anaerobes and for the isolation of some strains of pneumococci."

Bacteriologic Technic and Results.—"Films of the pus were stained by Gram and Ziehl-Neelsen methods. In all cases aerobic and anaerobic cultures were made on horse-blood agar plates and in ox-serum broth. When examination suggested the need for enriched or selective media, Fildes' agar, 20% ox-serum agar, or horse-blood agar with crystal violet (1 in 500,000) or sodium azide (1 on 1,000) were used."

Only 1 abscess was sterile; only in 1 case of traumatic abscess, due to Str. pyogenes, did later specimens prove sterile.

Comment (McFarlan).—"It appears . . . that more than one species of organism was present in a large proportion of the abscesses from which anaerobic organisms were isolated. . . . It is possible that the use of agar in the inoculum was responsible for the production of abscesses in rabbits' brains with anaerobic streptococci and fusiform bacilli by Falconer and others.[246] (1943). It seems therefore quite probable that brain abscesses due to anaerobic organisms originate in foci of

245. Sanford, H. N.: Abscess of Brain in Infants Under 12 Months of Age: Report of Two Cases with Seventeen Collected Cases, Am. J. Dis. Child. **35**:256-261 (Feb.) 1928.

246. Falconer, M. A.; McFarlan, A. M., and Russell, D. S.: Experimental Brain Abscesses in Rabbit, Brit. J. Surg. **30**:245-260 (Jan.) 1943.

lowered O-R potential (Fildes,[247] 1927) produced by a vascular accident or by aerobic organisms which later die out."

"There are repeated statements in the literature (Neumann,[248] 1909; Alpers, 1939; Grant,[249] 1941) that anaerobic and Gram-negative bacilli inhibit capsule formation. Histological examination demonstrated well-formed collagenous capsules in two cases in this series from which fusiform bacilli were isolated. . . . One of these cases has already been cited by Falconer et al (1943), who found that encapsulation occurred in brain abscesses caused by the intracerebral inoculation of fusiform bacilli or anaerobic streptococci in rabbits."

These observations agree with Atkinson's [250] (1934) statement that *P. vulgaris* is apparently not highly virulent in brain abscesses.

The Electroencephalogram in the Localization of Cerebral Abscess (Schwab and Carter [251]).

The electroencephalogram, or "brain wave," as the electroencephalographic tracing is called, was first developed by Prof. Hans Berger,[131] of Jena, Germany, in 1929. At first considered an artefact, it was established by Adrian in England, and first used by F. A. and E. L. Gibbs [252] in 1935 for the study of the electric discharges of the brains of epileptic persons.

Fifteen cases of proved cerebral abscess were examined by Schwab and Carter. In 7 an electric focus was shown which localized the abscess. "In seven others the brain waves were diffusely abnormal. In only one was a negative [electroencephalographic tracing] encountered, and in that the abscess was in the cerebellum."

In the group of cases in which Schwab and Carter felt certain of the localization, the follow-up study showed by operation or postmortem examination that electroencephalographic localization had been accurate in 85 per cent. In the group about which they were doubtful it had been accurate in 55 per cent. The score for the total number of cases in these two groups was 72 per cent. In the group in which the electroencephalograms had not shown any pathologic condition, the follow-up study revealed no intracranial lesion in 91 per cent.

Air encephalography on comparison was found to give 90 per cent accurate localizations. In cases in which it is suspected that cerebral abscess is complicating sinal or aural disease, air encephalography is useful. The examination is painless.

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247. Fildes, P.: Tetanus: Conditions Under Which Tetanus Spores Germinate in Vivo, Brit. J. Exper. Path. **8**:387-393 (Oct.) 1927.

248. Neumann, H.: Otitic Cerebellar Abscess, translated by R. Lake, London, H. K. Lewis & Company, 1909.

249. Grant, F. C.: Brain Abscess: Collective Review, Internat. Abstr. Surg. **72**:118-138, 1941; in Surg., Gynec. & Obst., February 1941.

250. Atkinson, E. M.: Abscess of the Brain, London, Medical Publications, Ltd., 1934.

251. Schwab, R. S., and Carter, R.: Electroencephalography in Relation to Otology, Laryngoscope **52**:757-767 (Oct.) 1942.

252. Gibbs and Gibbs, cited by Schwab and Carter.[251] Gibbs, F. A., and Gibbs, E. L.: Atlas of Electroencephalography, Cambridge, Mass., Lew A. Cummings & Co., 1941.

If an abnormal record is obtained, even if it is without localizing value, it is strong evidence of intracranial disease. Schwab and Carter [253] have made the encephalographic examination in the operating room after exposure of the brain.

Technic.—"Pathologic processes do not give off electric discharges. It is the surrounding brain which is having its normal metabolism interfered with." "The activity comes from a part of the brain which has been deprived of oxygen or of sugar." "If one can find places where the waves are opposite each other, one can see that the source is between these two large waves and that the disturbance must come from the electrode between them." Schwab and Carter [253] call that a "phase shift," and it is the means they use in localizing the process.

"The waves from the normal human brain are the alpha and the beta. The alpha waves disappear when the light is turned on and return when it is turned off. When the whistle blows, there is hardly any change in the rhythm. There are three types of abnormal activity. First there is the slowing of the rhythm from 10 per second down to 3 or 6 per second, with a greater build-up in the voltage. These waves, about five or six times higher in voltage and much slower than normal, are called delta type and are found in many clinical conditions, such as disease of the brain and deprivation of oxygen.

"The second abnormal type is a fixed frequency between 16 and 22 per second. The third type is a mixture of the first and second types. This consists of a three cycle wave, the delta wave and the fast wave,, and is found nearly always in epilepsy and can be used to diagnose petit mal" (Schwab and Carter [253]).

Aphasia.

Nielsen [254] and von Hagen, according to Cobb,[255] state that the "auditory sense has three levels" in the brain, each not clearly defined. The first level, the "primary auditory reception," is in the mesial geniculate [kneelike] bodies of the metathalamus [region of the diencephalon] It is a relay nucleus for the auditory pathway. "Each cochlea sends fibers to both geniculate bodies. Thence fibers go to the temporal lobes [level 2], where cortical areas . . . make the center for auditory recognition. . . . Since the innervation is bilateral, a single cerebral lesion cannot cause complete agnosia,[256] and even bilateral lesions never cause deafness."

Acoustic agnosia for sounds [absence of the ability to recognize the nature of sound] is not known to occur without acoustic verbal [oral word] agnosia, but in many cases of the latter the recognition for sounds is retained.

For example, a patient may have lost his knowledge of the meaning of word symbols but can still recognize a whistle, the sound of crumpling paper, etc., . . .

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253. Schwab, R. S., and Carter, R. A.: Electroencephalography in Relation to Otology, Arch. Otolaryng. **37**:282-287 (Feb.) 1943.

254. Nielsen,[112] cited by Cobb.[255]

255. Cobb, S.: Review of Neuropsychiatry, Arch. Int. Med. **68**:1232-1245 (Dec.) 1941.

256. Agnosia (ignorance), absence of the ability to recognize the form and the nature of persons and things, or of the perceptive faculty.

". . . Thus it is obvious that the acoustic mechanism is . . . concentrated in space in each temporal lobe but has less unilaterality in the dominant [cerebral] hemisphere than . . . the visual mechanism." In other words, the function of language is largely concentrated in the leading hemisphere, but a primitive sort of speech (emotional, expletive, habitual) is subserved in the homologous areas of the minor hemisphere.

As to recognition of learned symbols for words that are seen, the center is in the angular gyrus (Brodmann's area 39). "A lesion here causes visual verbal agnosia, or 'word blindness,' as opposed to the 'word deafness' resulting from a lesion in the temporal lobe."

In regard to objective nouns, the simplest and commonest words used, it is stated that "they are names, usually of objects seen; so engrams must be stored in Brodmann's areas 22 and 37 correlating both visual and auditory meanings. That this is true is shown by cases of temporal lobectomy in which the language formation area of the leading hemisphere is removed. The result is amnesic aphasia. The patient has lost the storage mechanism for nouns; his 'naming center' [Mills] is gone. When shown a pen he uses circumlocution and may reply 'It's to write with' but cannot say [or recall the noun] 'pen.' He is suffering from the symptom of anomia, one of the commonest subdivisions of aphasia, . . . in a way the opposite of motor aphasia."

["Naming aphasia" is the common aphasia seen in a right-handed person with temporosphenoidal abscess when the abscess is on the dominant left side. W. P. E.]

"Area 39 has the function of symbolic visual recognition, i. e., understanding letters and words by sight. Because words were first learned by hearing, however, area 39 cannot function if cut off from areas 41 and 42. During the process of learning to read," words are told or, more definitely, sounded out. "Thus the portion of the temporal lobe lying between areas 39 and 42 is of great importance. This takes in the posterior part of area 22 and the upper part of area 37. A lesion here may cause as much loss of reading ability (alexia) as a lesion directly in area 39. Moreover, because language is learned by associating vision and hearing with objects and symbols, this area is particularly important." Nielsen would call it "the language formation area." (See chart of Brodmann's areas.)

The entire conception of "temporal lobe anomia"—inability to name an object—was introduced by the supposition of Mills that the site of the "naming center" is the inferior temporal gyrus, just anterior to the middle of the inferior lateral border of the hemisphere (Santee).

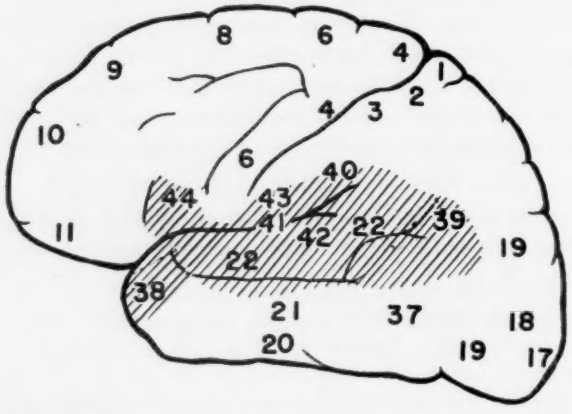
Kanzer [257] believes that in a lesion of the third temporal convolution, particularly an abscess, "word-finding difficulties may be an early sign."

"The third temporal convolution, because of its proximity to the tegmen tympani and tegmen antri, is exposed to infections spreading

257. Kanzer, M.: Early Symptoms of Aphasia with Brain Tumors, J. Nerv. & Ment. Dis. **95**:702-720 (June) 1942.

from the inner ear. The occurrence of word-finding difficulties with abscesses in the area . . . provides another instance that the earliest sign of a developing aphasia . . . is frequently, if not always, an amnesic [258] [*αμνησια*, forgetfulness] aphasia. In later stages of brain abscesses involving the temporal lobe, the language disorder is that of a sensory aphasia [259] (Bonvicini)."

Summarizing, Kanzer states: "It appears that amnesic aphasia represents a mild disturbance affecting the association functions of language. There is clinical evidence that two regions of the brain are particularly involved . . ., namely, the area of Broca [260] [the speech center situated in the third left frontal convolution in right-handed persons] and the zone adjacent to the sensory center for sound in the temporal lobe of the dominant cerebral hemisphere . . . may be part of a more extensive common language area about the fissure of Sylvius."



A diagram of the left cerebral hemisphere showing the location of histologically recognizable areas (after Brodmann). The shaded zone includes areas involved in language. Areas 4 and 41 lie largely in the depths of the fissures. (After Cobb.[255])

One of my (W. P. E.) patients suddenly manifested a sensory (naming) aphasia which lasted for a few hours and then entirely disappeared. In reviewing this case I am inclined to believe that in many patients with adjacent temporosphenoidal abscess who later manifest aphasia, an incomplete form of aphasia is

258. Amnesia, inability to recall the name of an object or other word wanted to express an idea.

259. Sensory aphasia, loss of the power to comprehend written (or printed) or spoken words, gestures or signs; it includes word blindness, sign blindness, apraxia and word deafness. (Santee, H. E.: Anatomy of the Brain and Spinal Cord, ed. 5, Philadelphia, P. Blakiston's Son & Co., 1915).

260. Kanzer speaks of the area of Broca, "which is the parolfactory area," when he means Broca's center (Stedman, T. L., and Garber, S. T.: Stedman's Practical Medical Dictionary, ed. 14, Baltimore, William Wood & Company, 1939, p. 156).

present off and on for several days prior to its becoming sufficiently outspoken to command the attention of the patient or the physician.

In a right-handed man with an abscess in the left hemisphere the presence of a naming aphasia is pathognomonic. The aphasia in the early stages is apt to be transient, appearing suddenly and as suddenly disappearing. At the time of the examination the patient may talk well, but his family will state that on a certain date he was "out of his head." In a certain case careful questioning showed that the patient was unable to name an object which he wanted; after repeated attempts to name it, he got out of bed and got it for himself; in a few hours the aphasia had disappeared entirely.

Personal experience has taught me (W. P. E.) not to be deceived by an apparent improvement. In another case a young man, following two operations on the bulb of the jugular vein, suddenly became aphasic. When seen the following evening his speech was perfect, but after his physician had described the aphasia, I felt warranted in advocating a temporosphenoidal exploration. On account of the previous operation and the—at the time—excellent physical condition of the patient, his family refused. A few weeks later he presented himself to all appearances in perfect health. However, ophthalmoscopic examination revealed slight papilledema. The following summer he suddenly became comatose and died within a few hours from rupture of the abscess.

A "naming aphasia" is seldom complete until signs of compression develop. In the presence of aural suppuration which was preceded by a vague chill and is associated with headache an exploration of the temporosphenoidal lobe is demanded. Even though complete, the aphasia disappears entirely after operation, so that the tract cannot have been destroyed. The "naming" character of the asphasia, however, although incomplete, usually can be demonstrated if properly investigated. Frequently it can be elicited only by careful questioning.[261]

Accidental Finding of Air in a Routine Examination of the Skull Produces a Diagnosis of Abscess of the Brain.

Kleinfeld's [262] case merits attention because of the rapidity with which empyema of acute frontal sinusitis accompanying mild rhinitis was followed by an abscess of the frontal lobe of the brain.

The finding of air in the cerebral ventricles in a routine roentgenographic examination of the skull suggested the possibility of a communication of the frontal sinus with an abscess.

Culture of the nasal secretion and the abscess showed the beta hemolytic streptococcus and staphylococcus.

"Given a case of frontal sinusitis with a sudden change for the worse (without there being evidence of a meningitis or of an osteomyelitis to account for such an exacerbation), the possibility of a frontal

261. Eagleton,[21] pp. 177-178.

262. Kleinfeld, L.: Abscess of the Frontal Lobe Secondary to Frontal Sinusitis: Operation and Recovery, J. Mt. Sinai Hosp. **9**:96-99 (July-Aug.) 1942.

lobe abscess must be considered. If there are, in addition, psychic changes, the probability of such an abscess is greater."

Abscess of a Frontal Lobe from an Infected Mucocele, Associated with an Osteoma of the Ethmoid Bone; Treatment of an Unsuspected Abscess of the Brain; Proliferating Cyst from Mucous Membrane.

Hamby's [263] case of osteoma of the ethmoid bone with an accompanying intracranial mucocele presented the problem of an abscess of the brain unsuspected before exposure.

Two years after sustaining a laceration of both supraorbital ridges, the patient, 24 years old, experienced emesis followed by left frontal headaches. During the three weeks prior to hospitalization, July 25, 1938, he lost 18 pounds (8 Kg.). He was unable to smell.

Examination showed slight tenderness of the left side of the forehead. The optic disks were edematous, with hemorrhages and exudates. There was slight paresis of the lower part of the right (opposite) side of the face. Both knee jerks were sluggish. A suggestive Babinski sign was noted on the right side. Lumbar puncture revealed a clear normal fluid.

Roentgenographic examination showed a tumor, 3.5 by 2.5 cm. in size, projecting from the left frontal or the ethmoid sinus into the floor of the anterior fossa.

Aug. 1, 1938, frontal craniotomy was performed on the left side. The dura was relaxed by intravenous administration of 100 cc. of 50 per cent dextrose solution and retracted, revealing an osteoma growing upward into the anterior fossa. The dura was tightly adherent to the tumor. It was decided to remove the supposed mucocele before attacking the osteoma.

Technic of Sealing Off an Infected Tract.—Exploration revealed a large, smooth-domed, pinkish gray, cystic mass about 1 cm. below the surface. Ten cubic centimeters of creamy yellow pus was aspirated. The needle was touched with the electrocoagulating current as it was removed, thus sealing off its tract. Staphylococcus aureus was present in the pus.

At a second operation the dome of the abscess capsule presented in the wound and was transfixed with fine chromic catgut sutures. The capsule was opened with the electrosurgical blade; the capsule was easily separable from the brain but was firmly attached at the base.

After operation the increased intracranial pressure was relieved by daily lumbar punctures. The decompression wound still bulged, which caused the belief that it was necessary to attack the lesion at the base.

A third operation was undertaken forty-six days after the original operation: The dura was separated from the frontal bone. About 20 cc. of pus drained from the subdural space, the abscess leading down to the osteoma. The abscess capsule was removed. The dura was elevated from the osteoma. Complete removal of the osteoma was not done because of the presence of infection, which precluded the use of a fascial graft, which would have been necessary to separate the nasal cavity from the dura.

Histologic examination of the abscess capsule revealed "columnar mucous epithelium in some areas."

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263. Hamby, W. B.: Orbitoethmoidal Osteoma with Infected Intracranial Mucocele, Arch. Otolaryng. **36**:510-513 (Oct.) 1942.

Sept. 6, 1940 the depressed cranial defect was repaired with an osteoperiosteal graft taken from the tibia.

September 25 the patient was readmitted because of jacksonian convulsive seizures starting in the right side of the body and occurring every thirty minutes. On the following day an encephalographic examination disclosed mild dilatation of the frontal horn of the left lateral ventricle and a suggestion of a porencephalic cyst under the bone defect.

Cushing reviewed cases of orbitoethmoidal osteoma with infected intracranial mucocele in 1927. Kessel [264] collected 15 cases with pneumatocele from the literature.

Comment (W. P. E.).—Every patient with osteoma of the frontoethmoid angle on whom I have operated has also had a closed empyema of the frontal sinus, so that I have come to regard the osteoma as being caused by the suppurative process irritating the bone in this highly osteogenic area.

The intracerebral abscess in Hamby's patient was probably due to a fracture of the inner plate of the frontal sinus from the injury of the supraorbital ridge two years previously. Through the fracture, proliferating mucous membrane grew, as shown by the histologic examination of the capsule, which revealed "columnar mucous epithelium in areas." This proliferating mucous membrane cyst later became infected. The pathologic process was first described by me [265] in 1929.

Paralysis of Conjugate Gaze Ipsilateral to the Hemisphere Containing a Cerebellar Abscess.

Bucy and Weaver [266] observed paralysis of conjugate gaze in 3 of 7 verified cases of cerebellar abscess. The conjugate deviation of the eyes was directed away from the side on which the cerebellar abscess was situated. They state that this is a valuable aid in localizing cerebellar abscess.[267]

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264. Kessel, F. K.: Orbito-Ethmoidal Osteomata with Intracranial Complications: Report of a Case, Guy's Hosp. Rep. **89**:337-346, 1939.

265. Eagleton, W. P.: The Cerebrospinal Fluid as an Aid to Diagnosis and Treatment of Inflammatory Diseases, J. Laryng. & Otol. **44**:657 (Oct.); 721 (Nov.) 1939 (4 cases).

266. Bucy, P., and Weaver, T. A.: Paralysis of Conjugate Lateral Movement of the Eyes in Association with Cerebellar Abscess, Arch. Neurol. & Psychiat. **45**:568-569 (March) 1941.

267. Eagleton,[21] p. 197. Lateral deviation—the cerebellar component of nystagmus—generally occurs when compression or destruction is sufficient to cause abolition of the cerebral control. The author is of the opinion that compression sufficient to cause coma and lateral deviation is much more easily induced in cerebellar than in cerebral abscess. When otitis media is the primary focus of an abscess of the brain, the appearance of lateral deviation of the eyes should be regarded as evidence that the posterior fossa is the site of the infection, since an abscess of the adjacent temporosphenoidal lobe cannot cause spontaneous lateral deviation of the eyes.

In each case there was paralysis of conjugate lateral movement of the eyes to the side of the abscess, and in 2 cases there was spontaneous conjugate deviation of the eyes away from the side of the lesion as well.

Paralysis of conjugate lateral movement of the eyes produced by a lesion in the posterior fossa is always ipsilateral to the lesion.

Cerebellar Abscess in Children; Recurrent Meningitis Five Years Later.

Nine cases of cerebellar abscess following mastoidectomy, with seven recoveries, are reported by Schreiber.[268] In 2 cases there had to be a second operation.

Technic.—"Operative treatment . . . was delayed as long as possible . . . to allow the abscess wall to thicken and the acute symptoms of meningitis and cerebritis to subside." The operation was performed under local anesthesia. A trephine opening "was made over the suspected cerebellar lobe with a Hudson burr, midway along the line between the occipital protuberance and the mastoid tip [ordinarily about one-half inch below the transverse sinus]. The dura was incised one-fourth inch to allow insertion of a blunt cannula with a side opening." The wound was closed with silk.

Recurrent Meningitis Five Years After Successful Drainage of an Abscess.—In case 1, a girl aged 9, after five years of apparently normal health following evacuation of a greenish pus-filled cerebellar abscess from which Streptococcus haemolyticus was isolated, had a stiff neck. Pneumococci were isolated from the blood and the spinal fluid. The patient died four days later from septicemia and meningitis.

The author's only comment is that it "is just another illustration of the variable immunity of the central nervous system to different types of organisms."

Comment (W. P. E.).—It is to be noted that the cerebellar abscess was of staphylococcic origin and that the meningitis four years later was pneumococcic. I am of the opinion that the terminal meningitis originated not from the original infection in the ear but from a latent infection of the sphenoid sinus.[269]

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268. Schreiber, F.: Cerebellar Abscesses of Otitic Origin in Nine Children: Eight Recoveries After Cannulation, Ann. Surg. **114**:330-335 (Sept.) 1941.

269. Eagleton, W. P.: Suppurative Meningitis of Otitic and Nasal Origin: Its Relation to Blood Stream Invasion of the Pial Vessels, Arch. Otolaryng. **15**:885-905 (June) 1932. "Pneumococcus type III meningitis secondary to infection of pial vessels is generally of sphenoidal origin in my experience. In the acute cases, the route of the infection into the meninx is by blood vessels, the primary vascular lesion being microscopic; in the more protracted cases, the sphenoidal basis is the seat of a hematogenous osteomyelitis."

Eagleton, W. P.: Meningitis from Sphenoid, Tr. Am. Laryng., Rhin. & Otol. Soc. **38**:51-62, 1932; Meningitis from the Petrous Apex and the Sphenoidal Basis, Surg., Gynec. & Obst. **60**:586-587 (Feb., no. 2A) 1935.

Rarity of Abscess Within the Spinal Cord of Otitic Origin.

Among the 39 cases of abscess within the spinal cord collected by Arzt,[270] there were only 2 in which the abscess originated from infection of the middle ear (Schmitz, 1926; Nonne, 1925-1926).

Unusual Cases of Abscess of the Brain:

Abscess of the Temporosphenoidal Lobe Following Lempert's Fenestra Nov-Ovalis Operation for Otosclerosis.

Three weeks after Lempert's fenestra nov-ovalis was created in the left ear, the patient showed signs suggestive of an abscess of the left temporosphenoidal lobe. The abscess ruptured into the ventricles one week after the onset of symptoms. It was located and surgically drained. The patient died twelve hours after this intervention. A round window graft had been inserted in the same ear one year previous to this.

Another patient showed symptoms suggestive of embolism of the left temporosphenoidal lobe immediately after undergoing Lempert's [271] operation. The abscess drained without disturbing the postoperative fenestration field. Practical, serviceable hearing was restored and has been maintained ever since.

Cerebral Abscess Accompanying Congenital Heart Disease.

Cerebral abscess occasionally is a manifestation of congenital heart disease. The abscess generally is single and is in the right cerebral hemisphere. To 12 cases previously reported, Wechsler and Kaplan [272] add 2 of their own.

These 2 cases and 1 other were the only instances in which the condition was recognized during life; in the others the anomaly was not even suspected. The condition usually was thought to be either cerebral embolism or thrombosis. Fever, leukocytosis, slow pulse and early modification of the ocular fundus suggest an infectious, expanding intracranial lesion. There is no adequate explanation of the mechanism of the production of "paradoxic" cerebral abscess. It has been stated that this condition can occur when there is a defect in the ventricular system with dextroposition of the aorta. Another possible explanation is that vascular disease of the brain, with consequent encephalomalacia, prepares a focus which is receptive to infection.[273]

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270. Arzt, P. K.: Abscess Within the Spinal Cord: Review of the Literature and Report of Three Cases, Arch. Neurol. & Psychiat. **51**:533-543 (June) 1944.

271. Lempert, J.: Lempert Fenestra Nov-Ovalis with Mobile Stopple: A New Advance in the Surgical Treatment for Clinical Otosclerosis Evolved as a Result of a Research Study of One Thousand Cases in Which Fenestration Has Been Performed During the Last Seven Years, Arch. Otolaryng. **41**:1-41 (Jan.) 1945.

272. Wechsler, I. S., and Kaplan, A.: Cerebral Abscess (Paradoxic) Accompanying Congenital Heart Disease, Arch. Int. Med. **66**:1282 (Dec.) 1940.

273. Robbins, S. L.: Brain Abscess Associated with Congenital Heart Disease, Arch. Int. Med. **75**:279-283 (May) 1945.

Abscess of the Medulla Oblongata of Otitic Origin.

Weickhardt and Watts [274] report a case of "intramedullary abscess of the right dorsolateral portion of the medulla oblongata in the region of the right cerebellopontile angle, involving the lower portion of the pons."

The patient, aged 34, had noted intermittent discharge from the right ear since childhood. Sept. 16, 1942 he experienced pain in the right ear. The hearing of this ear was lost. In November pain in the region of the mastoid process and facial paralysis (right side) were relieved by simple mastoidectomy. In December there were recurrent paroxysms of meningeal irritation. In February there was persistence of symptoms and radical mastoidectomy was performed. March 10 there was a tendency to fall to the right on attempting to stand. The speech showed a gradually increasing bulbar quality. March 13 the right half of the palate was paralyzed. March 18 exploratory craniotomy disclosed no cerebellar lesion. The patient suddenly died of respiratory paralysis.

Necropsy showed the anterior surface of the right cerebellum adherent to the right petrous pyramid, the bone of which was soft and contained two sequestrums. There was an abscess in the region of the cerebellopontile angle. Its cavity extended into the substance of the brain stem, involving principally the right dorsolateral portion of the medulla oblongata and the right flocculus; it also extended into the lower portion of the pons.

A gross section through the medulla showed the abscess compressing medially such structures as the fasciculus solitarius, the descending root of the trigeminal nerve and the inferior olivary body. The corpus restiforme at this level was almost completely destroyed.

Microscopic examination of the petrous pyramid revealed small portions of necrotic bone in a matrix of granulation tissue, infiltrated with leukocytes.

The anatomic diagnosis was osteomyelitis of the right temporal bone and abscess of the brain stem.

Comment (W. P. E.).—This case is the tenth case of abscess of the medulla oblongata on record and the second case in which the infection originated from the ear (Egas Moniz [275]). An abscess occurring in the brain stem shows a tendency to form elongated cavities, so that several levels of segments are likely to be involved. Thus, in the 10 cases reported the abscess was limited to the medulla oblongata in only 3. In Bircher's,[276] Forget's [277] and Cassirer's [278] cases and in the

274. Weickhardt, G. D., and Watts, J. W.: Abscess of the Medulla Oblongata: Report of a Case, Arch. Neurol. & Psychiat. **51**:282-284 (March) 1944.

275. Egas Moniz: Abcès isolé du bulbe, Rev. d'oto-neuro-opht. **12**:568-570 (Sept.-Oct.) 1934.

276. Bircher, H.: Abscess in Medulla oblongata und Pons, Cor.-Bl. f. schweiz. Aerzte **11**:102-105 (Feb. 15) 1881.

277. Forget, C.: Note sur les rapports des symptomes avec les lesions encephaliques, Union méd. **4**:366 (July 27) 1850.

278. Cassirer, R.: Ueber metastatische Abscesse im Centralnervensystem: Isolierter metastatischer Abscess im Pons und in der Medulla oblongata, Arch. f. Psychiat. **36**:153-206 (Aug.) 1902.

case reported by Weickhardt and Watts it extended upward into the pons.[279]

Anaerobic Bacillus Fragilis the Cause of Multiple Metastatic Abscesses, Including an Unsuspected Cerebellar Abscess, as a Complication of Chronic Otitis.

In Newhart's[280] case, chronic purulent otitis media of the left side had continued for twenty-eight years. The discharge suddenly became bloody and was accompanied by pain in the ear. Chill, sweating and vomiting were followed by pain in the chest, an icteric condition of the scleras, a spiking temperature curve, rigidity of the neck and a positive Kernig sign. Blood culture yielded anaerobic hemolyzing colonies of long threadlike bacilli with purple granules, identified as Bacillus fragilis.

At operation cholesteatoma, an old perisinal abscess and an obliterated sinus containing foul-smelling pus were found. Pus from the mastoid process when cultured gave a growth of B. fragilis. At autopsy a cerebellar abscess was found on the right (the opposite side of the aural lesion). Old thrombi were present in the superior and petrosal sinuses; there were also two small abscesses in the liver.

B. fragilis can be isolated only by anaerobic culture.

Treatment of Abscess of the Brain.

Advances in Treatment: The Two Stage Method of Drainage (Kahn,[281] 1937).—In Asherson's[282] case 1 (otogenic meningitis secondary to acute mastoiditis) a latent abscess of the temporal lobe was treated by decompression and aspiration. At a subsequent recurrence the dura was incised, which was followed by spontaneous extrusion of the abscess and extensive postoperative hernia cerebri. This was treated by a rubber dressing, retained in situ for a long period.

Comment Two and Three-Quarter Years Later (Asherson).—"The late onset of otogenic meningitis [tenth week after apparent cure of the patient] indicates the possibility of other intra-cranial complications . . ., such as a temporal lobe abscess. . . .

"The incision of the dura enabled the abscess to be extruded apparently in toto, the delay of 14 days having enabled the abscess to rise to the surface."

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279. Eagleton, W. P.: Brain Abscess from the Standpoint of the Otolaryngologist, Laryngoscope **40**:336-356 (May) 1929; Tr. Am. Ophth. Soc. **34**: 64-68, 1929.

280. Newhart, H.: Report of Unusual Bacterial Findings in a Fatal Case of Chronic Otitis Media with Complications, Laryngoscope **49**:1024-1030 (Oct.) 1939; abstracted, Kopetzky, S. J.: Purulent Otitis Media, Mastoiditis, Sinus Thrombosis and Suppuration of the Petrous Pyramid, Arch. Otolaryng. **32**:962-993 (Nov.) 1940.

281. Kahn, E. A.: The treatment of Encapsulated Brain Abscess, J. A. M. A. **108**:87-91 (Jan. 9) 1937.

282. Asherson, N.: Temporal Lobe Abscess: Two Cases with Recovery; a Note on the Two-Stage "Kahn" Operation, J. Laryng. & Otol. **56**:347-363 (Oct.) 1941.

Time Taken for the Formation of the Capsule of an Otogenic Abscess of the Brain.—Eagleton (1928) dwells on the time taken for the formation of the capsule. The "capsular zone" which surrounds the abscess in its early days can be identified microscopically, but the macroscopic true capsule, which the surgeons place such stress on, takes a long time to form, before it can be identified within the brain substance by the blunt brain needle. According to Eagleton, the earliest time for the formation of a capsule 1 mm. thick is twenty-four days; that for the formation of a capsule 2 mm. thick is thirty-eight days.[283]

MENINGITIS

Analysis of Cases with Recovery.

Historical Survey of Cures.—In 1896 Jemma[284] reported one of the earliest cases of cure of pneumococcic meningitis.

In 1927 Goldstein and Goldstein[285] reported that "there are on record . . . about 150 cases of recovery from proved *pneumococcus meningitis.*" A review of the literature from 1936 to 1941 is presented by Ruegsegger.[286]

Otitis media and mastoiditis were the source of infection in 202 of 508 cases of meningitis, about 40 per cent.

Contagiousness of Pneumococcic Meningitis.—Ruegsegger states: "The disease occurred simultaneously in a man and his wife in the series [of cases] at the Cincinnati General Hospital, but both patients had lobar pneumonia, in addition. Boyd, Baron, and Schlachman[287] report . . . occurrences of primary Type II pneumococcus meningitis in a woman and her son, . . . one week apart."

Dominant Cell in Cerebrospinal Fluid.—In pneumococcic meningitis the dominant cell is the polymorphonuclear leukocyte, "but Malaguzzi-Valeri[288] reported a case of meningitis due to mouse-avirulent Type I pneumococci in which the cellular reaction of the cerebrospinal fluid was lymphocytic.

One Type of Organism Only.—Ruegsegger states that during the years 1936 to 1941 more than one kind of organism was never found in an infected spinal fluid at the Cincinnati General Hospital.

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283. Eagleton,[21] p. 48.

284. Jemma, R.: Un caso di guarigione di meningite cerebrospinale da diplococca di Fränkel, Gazz. d. osp. **17**:412, 1896.

285. Goldstein, H. I., and Goldstein, H. Z.: Pneumococcus Meningitis and Endocarditis, Internat. Clin. **3**:155-219 (Sept.) 1927.

286. Ruegsegger, J. M.: Pneumococcal Meningitis, Ann. Int. Med. **17**:693-713 (Oct.) 1942.

287. Boyd, L. J.; Baron, B., and Schlachman, M.: Recovery from Type II Pneumococcus Meningitis, New York M. Coll. & Flower Hosp. Bull. **1**:99-103 (June) 1938.

288. Malaguzzi-Valeri, O.: Considerazioni sull'eziologia della meningite linfocitaria benigna a proposito di un caso di natura diplococcica, Riv. di clin. pediat. **37**:520-534 (June) 1939.

Combined Treatment with Serum and Sulfonamide Compound.—Finland, Brown and Rauh [289] were the first to advocate a combined regimen of serum and sulfonamide compound for pneumococcic meningitis.

"Fast" Organisms.—In a few well authenticated cases the organisms have apparently become resistant or "fast" during the course of treatment.[290] Further chemotherapy is generally useless then, and serum treatment should be employed.

Several authors report that meningitis had its onset while a sulfonamide compound was being given for the primary infection.[291]

Results of Treatment.—At the Cincinnati General Hospital there is no record of a recovery prior to 1937.

The prognosis in infancy remains grave.

Influence of Bacteremia on Mortality.—Of the 296 recovered patients, only 31 had positive cultures. Of the 341 patients who died, 74 had bacteremia.

A Classification of Pneumococci of Meningitis into Types; Results of Treatment (Finland [292]).

"In 1932 Cooper and co-workers separated the unclassified strains of pneumococci, which had previously been included in group IV, into twenty-nine new types designated as types IV to XXXII."

Pneumococcic meningitis is "frequently caused by strains of the 'higher' types. Serum alone is probably of little or no value in the treatment of pneumococcic meningitis, regardless of the type of the organism. The reported results in collected series of cases of meningitis indicate that the mortality is the same in [patients] treated with sulfonamide drugs alone and in those in [whom] antipneumococcus serums are used in addition. . . . Such is also the case with pneumonia. There is good reason for believing that serum was of added benefit in those patients treated with the sulfonamide compounds.

289. Finland, M.; Brown, J. W., and Rauh, A. E.: Treatment of Pneumococcic Meningitis, New England J. Med. **218**:1033-1044 (June 23) 1938.

290. Ross, R. W.: Acquired Tolerance of Pneumococcus to M. & B. 693, Lancet **1**:1207-1208 (May 27) 1939. Germain, A.; Gautron, G., and Morand, P.: Phénomène de blocage de la sulfamide au cours du traitement d'une méningite à pneumocoques, Bull. et mém. Soc. méd. d. hôp. de Paris **56**:167-173 (May 9) 1940. Laur, O.: Ueber Pneumokokkenmeningitis, Med. Welt **13**:1483-1485 (Nov. 18) 1939. Court, D.: Pneumococcal Meningitis Refractory to M & B 693, Proc. Roy. Soc. Med. **32**:1206-1208 (Aug.) 1939.

291. Gubner, J.: Recovery of a Patient with Type III Pneumococcus Meningitis of Otitic Origin, Arch. Otolaryng. **28**:241-251 (Aug.) 1938. Escat, M.: Considerations sur deux cas de méningite otitique traités par les sulfamidés, Rev. de laryng. **60**:411-414 (May) 1939.

292. Finland, M.: The Present Status of the Higher Types of Antipneumococcus Serums, J. A. M. A. **120**:1294-1307 (Dec. 19) 1942.

"It is concluded that antipneumococcic serums of the higher types are effective and that they have a limited field of usefulness in the treatment of [patients] with pneumococcic meningitis of these types."

Pneumococci Have a Predilection for Extensively Pneumatized Bone.

The association of pneumococcus type III with otitis media was studied by Persky,[293] who reviewed 307 cases of otitis media in which mastoidectomy was performed (from June 1, 1935 to Jan. 1, 1940). Pneumococcus was found in 10.8 per cent of the 307 cases—in 33, or 17.3 per cent, of the 190 cases in which cultures were positive. Five deaths occurred in the 33 cases of pneumococcic meningitis. Persky states that Pneumococcus seems to have a "predilection for the extensively pneumatized bone."

Sulfonamide Compounds of Little Value in Necrosis of Bone.—The sulfonamide compounds are held to be of little value for acute otitis and mastoiditis due to Pneumococcus when actual necrosis of bone has occurred.

Fatal Complications of Pneumococcus Type III Otitis with Labyrinthitis (Altmann and Waltner [294]).—"The peculiar tendency of Pneumococcus type III infections to form a deep abscess of the posterior fossa . . . is well known. . . . In cases with mastoid involvement the initial symptoms are followed by a period in which the disease remains in a latent stage. It seems to subside but progresses actually into the mastoid process and even beyond . . . without causing alarming clinical symptoms. It becomes manifest only after cortical perforation or development of an intracranial complication. . . . Among 290 operative cases in Vienna, Austria, 58 per cent showed the protracted course (Altmann [295]). In the United States . . . Maybaum and Druss [296] observed it in only 22 per cent of their cases. . . .

"In case 1 the breaking through the labyrinthine capsule was apparently immediately followed by purulent labyrinthitis and by invasion of the leptomeninges, the bacteria advancing through the internal auditory meatus. . . . Only drainage of the labyrinthine cavities themselves could have been successful.

"In case 2 most probably the break-through occurred five weeks after the onset of the infection, shortly before or at the time when the

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293. Persky, A. H.: Pneumococcus Type III in Otitic Infections, Arch. Otolaryng. **34**:473-484 (Sept.) 1941.

294. Altmann, F., and Waltner, J. G.: Labyrinthitis Due to Pneumococcus Type III: Histopathologic Studies, Arch. Otolaryng. **40**:75-91 (Aug.) 1944.

295. Altmann, F.: Zur Pathologie und Klinik der akuten Mastoiditis, Monatschr. f. Ohrenh. **70**:1465-1492 (Dec.) 1936.

296. Maybaum, J. I., and Druss, J. G.: Otitic Infections Due to the Pneumococcus Type III, Arch. Otolaryng. **30**:21-37 (July) 1939.

signs of serous labyrinthitis became manifest. At this stage simple mastoidectomy was performed, but the diseased retrolabyrinthine cells were not sufficiently drained. The serous labyrinthitis progressed into diffuse purulent infection. The latter was followed by formation of an abscess in the fundus of the internal auditory meatus. The demarcation toward the medial part of the internal auditory meatus was not as yet very strong, and the spread of the infection toward the leptomeninges was only temporarily stopped. The longer duration of the labyrinthitis is proved by the fact that the annular ligament of the stapes and the membrane of the round window were destroyed and that in some places osteoclastic destruction of bone was taking place on the inner surface of the semicircular canals. In addition . . . there was a spread of the infection to the leptomeninges from an epidural abscess of the posterior fossa by penetration of the dura in that region. The meningeal signs appeared only a few hours before the death of the patient.

"In case 3 the symptoms of serous labyrinthitis developed seven weeks after the onset of the middle ear infection. At that time probably a labyrinthine fistula had already been present and a serofibrinous exudation into the perilymphatic space was taking place. Shortly thereafter the break-through was walled off and the symptoms subsided. Simple mastoidectomy was performed, but the diseased infralabyrinthine cells were not sufficiently drained. Six weeks later diffuse purulent necrotizing labyrinthitis developed which through the vascular and nerve channels of the vestibule and the cochlea rapidly led to diffuse leptomeningitis. The complete absence of clinical signs of meningitis deserves particular mention. . . .

"The labyrinthitis in . . . cases of infection with Pneumococcus type III is usually caused by the pneumococci breaking through the wall of one or several semicircular canals. Most frequently the posterior vertical canal is affected, and the break-through is preceded by the formation of a deep abscess of the posterior fossa. The latter, in turn, develops from infection of perilabyrinthine cells, most frequently from infection of the retrolabyrinthine group, and leads almost invariably to the formation of an epidural abscess of the posterior fossa.

Pathologic Observations.—"There is only a short initial exudative inflammatory stage. It is followed by a predominantly proliferative inflammation of the mucosa of the middle ear, with early and marked proliferation of the connective tissue but with only moderate swelling and hyperemia. . . . There is a well marked tendency toward organization of the exudate by way of ingrowth of young connective tissue, which leads to extensive formation of areas of organized tissue. These masses of newly formed tissue fill out the recesses of the middle ear cavity and surround the chain of ossicles. These changes cause the

marked conduction deafness, which recedes only slowly; they account also for a common observation in otitis caused by Pneumococcus type III, the lack of improvement in hearing after air inflation in a patient with a clinically subsiding infection of the middle ear. These histologic changes . . . are somewhat similar to those described by Wittmaack [297] as 'hyperplastic constitution' of the mucosa of the middle ear. . . . In a considerable percentage of cases (72 per cent, Wirth; [298] 83 per cent, Page [299]) the infection of the middle ear subsides spontaneously. In others the mastoid cells become infected while the infection of the middle ear continues or gradually recedes."

CASE 1.—*Summary.*—"A 28 year old patient had recurrent right-sided middle ear infections for twenty years. The last infection started two and a half months before hospitalization and produced few symptoms throughout the time; however, labyrinthine meningitis suddenly developed and the patient died within four days.

"Histologic examination showed that from infected cells in the anterior part of the sinodural angle an epidural abscess of the posterior fossa had developed which by an anterior approach had broken into the superior vertical canal in two places, causing purulent labyrinthitis. The labyrinthitis spread through the internal auditory meatus to the leptomeninges. The left ear showed meningogenic seropurulent labyrinthitis."

CASE 2.—*Summary.*—"In a 66 year old patient with acute purulent otitis media and mastoiditis of six weeks' duration signs of serous labyrinthitis developed. Simple mastoidectomy was performed, and a well pneumatized mastoid process filled with granulations was found; a large retrolabyrinthine cell . . . was opened. Three weeks later, after an uneventful postoperative course, signs of purulent meningitis suddenly developed, and the patient died a few hours later.

"Histologic examination showed that from the incompletely drained retrolabyrinthine cells a large epidural abscess had formed which broke through the posterior vertical canal into the labyrinth and led to purulent labyrinthitis, to formation of an abscess in the fundus of the internal auditory meatus and to subsequent meningitis. In addition the infection spread to the leptomeninges directly through the dura of the posterior fossa. From other diseased perilabyrinthine cells rarefying osteitis of the labyrinthine capsule had developed, which eroded the lateral semicircular canal."

CASE 3.—*Summary.*—"A 63 year old patient with acute otitis media and mastoiditis was operated on when after seven weeks serous labyrinthitis developed. Six weeks later, after an uneventful postoperative course, the patient suddenly presented signs of diffuse purulent labyrinthitis and died after three days without showing any meningeal signs.

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297. Wittmaack, K., in Henke, F., and Lubarsch, O.: Handbuch der speziellen pathologischen Anatomie und Histologie, Berlin, Julius Springer, 1925, vol. 12, p. 200.

298. Wirth, E.: Studien zur klinischen Bakteriologie der akuten Mittelohrentzündung, Beitr. z. Anat., Physiol., Path. u. Therap. d. Ohres **26**:190-232 (Dec.) 1927.

299. Page, J. R.: Bacteriology of Acute Infections of the Middle Ear and Mastoid, Arch. Otolaryng. **20**:447-451 (Oct.) 1934.

"Histologic examination disclosed that in the insufficiently drained retrofacial cells a large abscess had originated which extended to the posterior fossa and led to the formation of a large epidural abscess. This abscess had eroded the lean end of the posterior vertical canal and had broken into the labyrinth causing purulent, necrotizing labyrinthitis with subsequent leptomeningitis."

In the 3 cases described a deep abscess of the posterior fossa led to an infection of the labyrinth by breaking into one of the semicircular canals. Relatively frequently, however, the infection progresses through the dura of the posterior fossa to the leptomeninges without affecting the labyrinth.

CASE 4.—*Summary.*—"In a 45 year old patient left-sided otitis media developed, which seemed to clear up within a few days after myringotomy. Two months later he suddenly presented signs and symptoms of purulent meningitis (drum membranes were normal!) and died a few hours later.

"The histologic examination showed in the middle ear only few remaining signs of acute infection. The mastoidal pneumatization was well developed. The cells in the anterior part of Trautmann's triangle and the retrolabyrinthine cells had been transformed into a big abscess cavity. The capsule of the lean end of the posterior vertical canal had been eroded, but this process had come to a standstill. Progressive erosion of the internal cortical layer had led to formation of an epidural abscess of the posterior fossa from which the infection spread to the leptomeninges and from there to both labyrinths."

CASE 5.—*Summary.*—"Simple mastoidectomy was performed in a 65 year old patient because of right-sided acute otitis media with mastoiditis. The mastoid process was well pneumatized, and a large epidural abscess in Trautmann's triangle was found. Ten days later, after an uneventful postoperative course, septicemia and purulent meningitis developed.

"The histologic examination showed the perilabyrinthine cells well developed and infected. A slowly progressive granulating inflammation in the cells of the anterior part of Trautmann's triangle and in the retrolabyrinthine cells had extended forward around the posterior vertical canal and, after destroying the intercellular septums, had produced a big abscess on the outside of the internal cortical layer of the posterior fossa. By way of rarefying osteitis the capsule of the ampullated end of the posterior vertical canal had been eroded but not perforated. The internal cortical layer had been perforated in two places, and an epidural abscess of the posterior fossa had been formed which extended upward into the neighborhood of the superior petrosal sinus, with subsequent thrombophlebitis of the sinus. A purulent infiltration of the dura had led to diffuse leptomeningitis with beginning bilateral serofibrinous meningogenic labyrinthitis."

Comment (W. P. E.).—In rereading the "subsequent history" in these cases I am impressed with the lack of observation of the cardinal symptoms of chronic sepsis of bone: (1) slight irregular temperature, (2) sweating at night and signs of dural irritation, (3) headache and (4) corneal anesthesia, all of which I described in papers published 1929 through 1931.[300]

300. Eagleton, W. P.: Unlocking of the Petrous Pyramid for Localizing Bulbar (Pontile) Meningitis Secondary to Suppuration of the Petrous Apex, Arch. Otolaryng. **13**:386-422 (March) 1931.

"Points of Venous Vulnerability to Infection" from the Ear into the Meninges.

Steurer [301] found that persistent vascular connections often form a link from the region of the mastoid antrum to the posterior part of the sinus-dura angle; some vessels may open into the dura more anteriorly. Persisting vascular connections were observed mostly in patients with a dense mastoid process containing few, if any, air cells.

The diameter of the vessel varies from the size of the "finest of sewing thread to that of a knitting needle"; the length ranges from 2 to 7 mm.

Comment (W. P. E.).—The minute venous plexuses were described and named "points of venous vulnerability" in 1929.[265]

Advances in an Understanding of the Pathways of Infection from the Ear and the Protective Reactions.

Perlman and Lindsay [302] in a series of papers studied the petrosas of 58 temporal bones from 30 patients who had died of meningitis. In 15 of 28 patients studied by Lindsay the meningitis occurred as a complication of acute otitis media. In 9 of the 15 patients the route of infection could be definitely traced by histologic examination. In 1 patient, who was diabetic, Pneumococcus type III meningitis was secondary to acute labyrinthitis with suppuration of the endolymphatic sac; it had then invaded the leptomeninges.

Pathologic Observations.—"The predominating pathological lesion . . . was a suppurative process within pneumatic spaces (coalescent osteitis), which had produced destruction of cell partitions and had eroded through the cortex either directly or along preformed vascular channels in the bone, to the middle or posterior cranial fossa or both. . . . Considerable osteogenesis had occurred in granulation tissue, both in the lining of infected pneumatic spaces, and in adjacent marrow spaces, also in the granulating walls of the abscess cavity, and on the inner surface of the bony cortex beneath the dura. The one possible exception . . . was where a localized abscess was found, apparently in bone marrow. However, in close proximity to the abscess were a group of pneumatized spaces with a marked inflammatory reaction and osteogenesis within their walls. . . . The most significant feature was the evidence that the suppuration had remained localized for a considerable period before the development of the diffuse meningitis or the panotitis, and might during that time have been amenable to surgery. . . .

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301. Steurer, O.: Ueber die Bedeutung persistierender Gefässverbindungen zwischen Mittelohrräumen und Dura für die Entstehung der Meningitis, Hals-, Nasen- u. Ohrenarzt (Teil I) **30**:44-50 (Jan.) 1939; cited by Richardson, J. R., and Holmes, E. M.: Anatomy and Physiology of the Ear, Arch. Otolaryng. **32**: 793-818 (Oct.) 1940.

302. Perlman, H. B., and Lindsay, J. R.: Relation of the Internal Ear Spaces to the Meninges, Arch. Otolaryng. **29**:12-23 (Jan.) 1939; abstracted, Williams, H. L., and others,[307] p. 839. Lindsay, J. R.: Suppuration on the Petrous Pyramid, Ann. Otol., Rhin. & Laryng. **47**:3-36 (March) 1938; abstracted, Williams, H. L., and others,[307] p. 840.

Marrow of Petrous Bone.—"It is well known that there is free communication between marrow spaces and the mucosa of pneumatic cells and the mastoid antrum in the young child, . . . In the presence of a confined focus of suppuration in either the retrolabyrinthine or apex cells the bone marrow of the apex usually showed a definite reaction. This reaction may be described as a fibrosis, which starts along the periphery of the marrow spaces adjacent to the supporting focus, and soon becomes diffuse throughout the apex. The type of reaction found was the same in gray or fat marrow and in red marrow. The process begins as a dilatation of vascular spaces, followed by the appearance of young fibrous connective tissue and infiltration by plasma cells, macrophages and lymphocytes. Osteogenesis had occurred in several cases, in areas surrounding the focus of suppuration and bone absorption. . . . This type of reaction bears no histological resemblance to the hyperplasia of bone marrow occurring in response to systemic infections or in certain diseases of the hematopoietic system, but is an inflammatory reaction which has taken place in bone marrow adjacent to a walled-in focus of suppuration of coalescent osteitis. The destructive process in the focus has destroyed cell partitions and sometimes encroached on marrow spaces, but the reactive process within the marrow has been adequate to prevent extension in that direction and the suppuration had progressed along . . . vascular channels."

Labyrinthine Disease Leading to Meningitis.—This study suggests that in labyrinthitis with secondary meningitis the causative organisms invade the perilymphatic spaces first.

Perlman and Lindsay publish sections showing that the earliest manifestation of the invasion of the labyrinth is "a collection of inflammatory pus cells in the subarachnoid space about the seventh and the eighth cranial nerve in the internal auditory meatus, without destruction of the arachnoid."

Second, there is an invasion of the cochlear aqueduct with an appearance of pus cells about its opening into the scala tympani, without destruction of the arachnoid meshwork in the aqueduct.

Original Surgical Anatomic Observations.—"A . . . subarachnoid space can usually be traced to the mouth of the foramen for the facial nerve in the internal acoustic meatus, sometimes as far as the geniculate ganglion. . . . Usually just beyond the [facial] foramen the pia-arachnoid becomes closely applied to the trunk of the facial nerve to form its perineurium, effecting a barrier to pus cells extending along the facial canal. . . .

"There is a similar distribution of the arachnoid about the branches of the eighth nerve. At the foramens in the internal auditory meatus the arachnoid and the dura unite, and the arachnoid continues as the perineurium, obliterating the subdural and subarachnoid spaces.

"In these early stages of meningitis the fluid in the perilymphatic spaces exhibits an increased affinity for the eosin stain, which indicates that early chemical changes have taken place. This reaction makes its appearance first in the scala tympani adjacent to the round window and

in later stages involves the perilymphatic spaces more generally, at which time they stand out in contrast to the endolymphatic spaces."

Merbromin (Mercurochrome) Diffuses from Nose into Brain in Living Subject (Ross and Hamilton [303]; Lawton and Ross [304]).

Experimental Paths of Infection from the Ear.—Ross and Hamilton demonstrated that merbromin N.N.R. placed in the middle ear would penetrate the entire cochlea.

Experimental Paths of Infection from the Nose.—"The olfactory mucous membrane is highly absorptive for many types of particulate matter and for many viruses. Faber [305] . . . demonstrated that the definite anatomic channels of nasal absorption are the same as those by which materials placed in the subarachnoid space gain exit from the cranial cavity. Aqueous solutions have been proved to pass both along olfactory nerve sheaths and to cervical lymphatics, while the viruses of poliomyelitis, herpes simplex, yellow fever and vesicular stomatitis and louping ill are neurotropic and enter the central nervous system by growth either along the axis-cylinders or in the perineural spaces of the olfactory nerves; presumably not through lymphatic channels" (Lawton and Ross [304]).

The experiments of Lawton and Ross show "that mercurochrome penetrates and diffuses through the nasal mucosa . . . into the cranial cavity [in the living animal]. It apparently follows no definite path, but diffuses in all directions from the frontal sinus and nasal antrum into the soft tissues, to the dura mater and even onto the tips of the frontal poles of the brain. . . . Since the area of spread is so limited . . . it would seem that the spread of mercurochrome is not confined to lymphatic and blood vessels but occurs through the intervening tissue spaces, as suggested by Weed.[306] Staining "did not occur in dead animals," which indicates that "the movement of tissue fluids is essential for the penetration."

Comparison of the Frequency of the Cures of Otitic Meningitis Before and After the Advent of Treatment with Sulfonamide Compounds.

To evaluate the results of the treatment of otitic meningitis with sulfonamide drugs, Williams and co-workers [307] studied (1) patients

303. Ross, E. L., and Hamilton, J. W.: Penetration of the Inner Ear by Mercurochrome, Arch. Otolaryng. **29**:428-436 (March) 1939.

304. Lawton, A. H., and Ross, E. L.: Penetration of Perinasal Tissue by Mercurochrome, Arch. Otolaryng. **32**:853-858 (Nov.) 1940.

305. Faber, W. M.: Nasal Mucosa and Subarachnoid Space, Am. J. Anat. **62**:121-148 (Nov.) 1937.

306. Weed, L. H.: Studies on Cerebrospinal Fluid, J. M. Research **31**:51-118 (Sept.) 1914; The Cerebrospinal Fluid, Physiol. Rev. **2**:171-203 (April) 1922.

307. Williams, H. L.; Herrell, W. E.; Brown, A. E.; Kernohan, J. W., and Wagner, H. P.: Otitic Meningitis; A Review of the Literature and Report of the Results Five Years Before and Since the Introduction of Chemotherapy [in the Mayo Clinic], Laryngoscope **52**:835-869 (Nov.) 1942. They give their observation on pages 860 to 866.

who were treated before and (2) patients who were treated after the introduction of sulfonamide drugs.

Group 1: Of a total of 46 patients with meningitis treated before the introduction of sulfonamide drugs, 10 had fulminating meningitis; all 10 died. Among the remaining 36 patients there were 16 recoveries and 20 deaths, a recovery rate of 35 per cent.

"In other words, before the advent of chemotherapy a patient with meningitis had approximately three chances out of 10 for recovery."

Group 2: In the five years during which sulfonamide compounds have been available, of 24 patients suffering from otitic meningitis and treated with these drugs, 6 had fulminating meningitis; 4 of the 6 died and 2 recovered. (In 2 patients the meningitis developed postoperatively, and in both there was associated apical petrositis.) Of the remaining 18, 7 died. Thus in the whole group of 24 patients the recovery rate was 46 per cent. Only 16 of the 24 patients received adequate chemotherapy; 11 of them survived. This represents a recovery rate of 69 per cent.

"Arachnoid Vessel Meningitis" by Vascular Channels.

Photomicrographs published by Kelemen [308] showed not only "that the pathologic processes . . . advanced through the dura to the arachnoid by dissolution of the dura to produce arachnoid-mesh meningitis, but also that propagation to the veins of the pia, by way of the vascular canals from the dura to the bone of the tegmen, to produce arachnoid vessel meningitis, may take place." [307]

Comment (W. P. E.).—The "points of venous vulnerability" to infection occur in small venous plexuses, the exact position of which was demonstrated on an injected cadaver in 1929.[265]

Drum Membrane Normal in Otitic Meningitis.

Burman, Rosenbluth and Burman [309] reviewed 160 consecutive cases of meningitis. In 3 of 38 cases of otogenic meningitis the drum membrane appeared normal and yet the mastoid bone was completely destroyed. Incidence: They found an otorhinogenic focus in 58, or 36.2 per cent; in 38 of these the meningitis was otogenic (69 per cent) and in 20 (31 per cent) it was rhinogenic. In only 9 of the 38 cases of otogenic meningitis and 5 of the 20 cases of rhinogenic type did the complication occur before the age of 16 years.

Frequency of Pneumococcic Infection.—Pneumococcic infection was the most common, which may be accounted for by the close association of the otologic

308. Kelemen, G.: Propagations of Inflammatory Processes Between Petrous Bone and Endocranium of "Frustrated" Form, Ann. Otol., Rhin. & Laryng. **48**:375-391 (June) 1939.

309. Burman, H. J.; Rosenbluth, M., and Burman, D.: Otorhinogenic Meningitis: A Report of Fifty-Eight Cases, Arch. Otolaryng. **35**:687-719 (May) 1942.

service with the pneumonia and pediatric services at the Harlem Hospital. Twenty-seven of the 38 cases of otogenic type and 10 of the 20 cases of rhinogenic type were pneumococcic.

Pneumococcic infection thus appears in almost 75 per cent of all cases of meningitis of otitic and 50 per cent of those of rhinogenic origin. Of the cases in which meningitis was attributed to infection of the ear, Pneumococcus type III was present in 9 and Streptococcus in 5.

Rhinogenic Meningitis Following Operation and Trauma.—Three of the authors' cases followed operative trauma, and 8, fracture of the skull.

Statistics in the Literature Showing the Importance of Trauma in Meningitis.—Eagleton [123] stated that nearly 50 per cent of all cases of rhinogenic meningitis followed intranasal operations, the meningitis being but a recrudescence of a former meningeal infection, as all the patients had a history of previous headache and often attacks of vomiting.

Brunner [310] reported death from meningitis following removal of nasal polypi. The infection traveled to the dura along the sheaths of the olfactory nerve.

Imperatori [311] reported 7 cases of rhinogenic meningitis following intranasal operation on the sinuses.

Fehr's [312] analysis of 417 cases of meningitis showed that in 20, or 4.8 per cent, the infection could be traced to a previous fracture of an accessory sinus or of the petrous pyramid. In 1 case the meningitis followed acute otitis six months after the accident, and in another case, three years after.

Unusual Types of Otitic Meningitis.

A case of Bacteroides [313] meningitis with recovery is presented by Ballenger, Schall and Smith.[314] The infection arose from chronic otitis media. Five such cases have recently been observed at the Massachusetts Eye and Ear Infirmary, with four recoveries. The importance of making a search for Bacteroides by anaerobic cultural methods in cases of meningitis of otitic origin is stressed.

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310. Brunner, H.: Zur Pathologie und Klinik der rhinogenen Meningitis, Ztschr. f. d. ges. Neurol. u. Psychiat. **157**:92-99, 1937.

311. Imperatori, C. J.: Differential Diagnosis of Suppurative Meningitis Caused by Paranasal Sinus Disease with Some Suggested Prophylactic Measures, Laryngoscope **47**:300-310 (May) 1937.

312. Fehr, A.: Zur Behandlung von Schädelbasisbrüchen bei Komplikationen von Seiten der Nasenbenhöhlen und des Ohres, Helvet. med. acta **4**:637-641 (Nov.) 1937.

313. Bacteroid—resembling bacteria.

314. Ballenger, J. J.; Schall, L. A., and Smith, W. E.: Bacteroides Meningitis—Report of a Case with Recovery, Ann. Otol., Rhin. & Laryng. **52**:895-901 (Dec.) 1943.

Proteus Vulgaris Meningitis from Otitis Media Requires Immediate Radical Removal of All Diseased Tissue That Is a Focus of Decomposition.

Bacillus proteus (Proteus vulgaris) is a frequent inhabitant of a chronically draining ear; however, it rarely becomes pathogenic. The organism generally is found in combination with Streptococcus and Staphylococcus.

Cragg [315] and Lothrop [316] report recovery of patients with meningitis due to Proteus vulgaris, secondary to otitis media; McKee [317] reports an additional case of Proteus septicemia from otitis media and mastoiditis. In 10 of the 18 cases of Proteus meningitis reported in the literature the source of infection was the ear; of the 10 patients, 7 died and 3 recovered, a mortality of about 66 per cent; most of the patients died within a few days.

In 3 of the 4 cases of abscess of the brain from B. proteus infection the invasion of the brain originated from otitis media, and in 1, from peritonsillar abscess; 2 patients recovered after surgical drainage of the abscess of the brain.

Cragg Case.—The patient recovered from meningitis due to B. proteus, secondary to chronic otitis media and mastoiditis and associated with thrombosis of the lateral sinus and pulmonary abscess. The organism was cultured from the blood, from the spinal fluid and from material removed from the ear, the mastoid process and a pulmonary abscess. Treatment consisted of (*a*) mastoidectomy, (*b*) ligation of the internal jugular vein, (*c*) resection of the ribs, (*d*) administration of sulfanilamide and sulfapyridine and (*e*) transfusions.

Bacillus proteus, first described by Hauseron in 1885, is an actively motile, gram-negative, non-spore-bearing organism. It grows readily at room temperature. It is hemolytic and proteolytic. It is widely distributed in nature, being found in almost all putrefactive matter of animal origin, in soil contaminated by animal excretions, in stagnant pools and in sewage. It is commonly found in the mouth, on the skin and in the urine and feces of normal persons.

Up to 1920 there was some doubt whether it was even pathogenic, and today the organism is regarded frequently as saprophytic; when pathogenic it is extremely toxic and capable of producing severe infections. It is frequently present in otitis media, cystitis, pyelitis and war wounds but rarely in meningitis.

Comment (W. P. E.).—In reviewing the cases of Proteus vulgaris infection I have come to the conclusion that when Proteus infection of

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315. Cragg, N. R.: Otitic Meningitis Due to Bacillus Proteus, Arch. Otolaryng. **34**:345-348 (Aug.) 1941.

316. Lothrop, O. A.: Otogenous Infection Due to the Proteus Bacillus, New England J. Med. **229**:867-868 (Dec. 2) 1943.

317. McKee, T. L.: Bacillus Proteus Infections, Arch. Otolaryng. **39**:398-402 (May) 1944.

the ear causes either meningitis or septicemia, unlocking of the petrous pyramid (without exploration of the apex) and draining of all infected venous sinuses should be done at once. For Proteus infection of the aural domain when it becomes virulent has a tendency to attack the venous sinuses, the same as Pneumococcus type III. Advanced osseous eradication is called for, because in Proteus infection the bone contains the foci of tissue decomposition, and as the bone has no mechanism to control the infection, all diseased tissue should be thoroughly removed. This view is supported by the fact that septicemia from infection of the urinary tract is the only condition which does not have a high mortality rate (McKee).

The radical surgical intervention should be associated with the administration of sulfapyridine, which McKee thinks is more effective than sulfanilamide.

Sugar's[318] *Case.*—"Bacillus proteus, commonly pathognomonic for the urinary tract and the intestine, is very rarely found as the causal organism for middle-ear infection. . . .

"In 1940 Neter and Chait . . . reported one case, in which culture . . . from the ear and the mastoid revealed streptococci, . . . overgrown by a gram-negative bacillus, . . ."

A boy 11 years old had "pain in the right ear for several days and discharge, headaches, giddiness and sickness for the last three weeks. The mother stated that he had had a discharging right ear for a long time."

Examination of the right ear (Dec. 5, 1942) showed "some bone tenderness over the anterior aspect of the mastoid tip." A polypus filled up the external meatus. Whisper was heard by the right ear at 1 foot (30 cm.) and by the left ear at 6 feet (about 2 meters). Weber's test (left ear) showed sound lateralized to the left. Rinne's test, both ears, was negative. Schwabach's test showed right ear "normal (?)" and left ear "normal."

December 6: The patient suffered from dizziness, vomiting in the morning and frontal headaches. Whisper was not heard by the right ear. Conversational voice was heard by the right ear at 9 inches (about 23 cm.). There was slight positive rombergism with a sway to the right.

December 7: There was slight spontaneous nystagmus to the right. The patient's temperature was still normal.

As a preliminary, polypus was removed in order to achieve better drainage. A sulfonamide drug was given, 1 Gm. every four hours. Whisper was not heard in the right ear; conversational voice was heard about 1½ feet (34 cm.). The nystagmus, which the day before had been directed to the right, changed to the left and was of the first degree. A radical mastoidectomy was decided on.

A large cavity was encountered, filled with debris and liquid pus. Necrosed material and granulations were followed up through the antrum into the middle ear. The dura of the middle fossa and the sinus were exposed and appeared to be normal. The horizontal canal was intact. The lumbar puncture failed to obtain fluid.

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318. Sugar, M.: Meningitis Following Mastoid Infection by Bacillus Proteus, J. Laryng. & Otol. **59**:146-149 (April) 1944.

The evening of the operation the temperature rose to 102 F. in spite of continued treatment with the sulfonamide compound and the next morning the boy was unconscious and had marked rigidity of the neck. He died the following day.

The culture yielded pure B. proteus. Smears from the pus taken at the post-mortem examination showed gram-positive cocci (probably streptococci) and gram-negative bacilli (B. proteus?), but no growth of these organisms was obtained.

"Surrounding the right internal meatus a thin layer of soft yellowish-green pus was found both external and internal to the dura mater. The leptomeninges . . . contained a small quantity of blood, . . . localized more particularly about the upper extremity of each Sylvian fissure."

One serial section showed three foci of accumulation of pus: in the middle ear, in the internal meatus and in the perilabyrinthine cancellous bone.

The microscopic examination revealed with certainty the route of infection.

Comment (W. P. E.).—In my opinion the meningitis was precipitated by the removal of the polypus and later by the "radical operation." If an unlocking operation had been performed and the areas of infection around the labyrinth removed at an early date, meningitis would probably not have developed.

Meningitis Due to Escherichia Coli[319] *from the Ear.*

Barrett, Rammelkamp and Worcester[320] found that in 13 of 108 cases of meningitis the infection originated from disease of the middle ear, in infants.

Apart from the middle ear, it is likely that the organisms invade the meninges from the blood stream. "Although many of the authors have not recorded the results of blood cultures, Fothergill and Sweet stated that in the majority of their cases there was a bacteremia. In several of the reported cases the mother harbored bacteria in the lochia and/or urine which were similar to the organism isolated from the meninges of the infected infant. A primary hematogenous infection suggests itself if such a focus is responsible. The role the gastrointestinal tract plays as a portal of entry is difficult to assess, since many infants have diarrhea during the course of metabolic disorders unrelated to meningitis.

"The striking predilection of meningitis due to Esch. coli for infants under 3 months of age presents a matter for speculation. It seems probable that the newborn infant has little resistance to infection caused by the colon bacillus. This is supported by the observation of Ravid

319. Escherichia coli, or Bacillus coli communis (Escherich), Escherich's bacillus (Theodore Escherich, German physician, 1857-1911). It is abundant in human feces and those of domestic animals and is pathogenic.

320. Barrett, G. S.; Rammelkamp, C. H., and Worcester, J.: Meningitis Due to Escherichia Coli: Report of Two Cases with Recovery Following Chemotherapy; Review of the Literature and Report of Experimental Studies, Am. J. Dis. Child. **63**:41-59 (Jan.) 1942.

that the blood of the fetus contains little or no agglutinins for the colon organisms. It would appear advisable, then, to give transfusions of whole blood to newborn infants with meningitis due to Ech. coli, thus adding the possible beneficial effect of antibodies."

Meningitis Caused by Friedländer's Bacillus from the Ear and Sinuses.

In an analysis of 29 reported cases of meningitis resulting from infection with encapsulated bacilli of Friedländer's group, Ransmeier and Major [321] observed "infections of the middle ear, mastoid and sinuses found in over half the adults" (12 cases).

"Chronic disease of the ear and sinus of many years' duration may provide the avenue for invasion of the meninges in adults, while the sinuses are poorly developed in infancy and would not be expected to be of importance in that period of life. In 2 of the adults extremely severe sinusitis with osteomyelitis of the bony walls of the frontal and maxillary sinuses was observed,[322] while in 1 case the cavernous sinus was involved secondarily to sphenoid sinusitis." [323] Of the 12 patients with meningitis from the ear and sinuses, 9 died and 3 recovered.

Influenzal Meningitis Complicated by Mastoiditis Has a High Mortality.

Scully and Menten [324] report 9 cases of influenzal meningitis. Associated mastoiditis was apparently the precipitating factor in the death of 3 (80 per cent) of the patients and a grave complication in 2 others (20 per cent), in which recoveries occurred, out of a total of 5.

It is a surgical dictum that mastoiditis has an unfavorable influence on the patient's chance of recovery, especially if mastoidectomy is delayed.

All the patients were treated with type B anti-influenzal rabbit serum and a sulfonamide drug, and some also received hydroxyethylapocupreine hydrochloride intrathecally.

Meningitis from Molds.

Meningitis due to pathogenic fungi is not a rarity. Freeman [325] in 1932 mentioned a case of meningitis caused by Saccharomyces [326] and reviewed 19 other cases of various causation.

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321. Ransmeier, J. C., and Major, J. W.: Friedländer's Bacillus Septicemia and Meningitis: Report of a Case and Autopsy, with an Analysis of Twenty-Nine Cases Collected from the Literature, Arch. Int. Med. **72**:319-328 (Sept.) 1943.

322. Dmochowski, Z.: Beitrag zur Lehre über die pathogenen Eigenschaften des Friedländer'schen Pneumococcus, Centralbl. f. Bakt. (Abt. 1) **15**:581-588 (April 27) 1894. Sicard, A., and Pluvinage, R.: Méningite à pneumobacilles de Friedländer, Presse méd. **45**:1800-1802 (Dec. 15) 1937.

323. Jassniger, K.: Der Pneumococcus Friedländer als Erreger der eiterigen Meningitis cerebrospinalis, Centralbl. f. Bakt. (Abt. 1) **30**:1-3 (July 12) 1901.

324. Scully, J. P., and Menten, M. L.: Treatment of Influenzal Meningitis with Anti-Influenzal Rabbit Serum and Sulfapyridine, J. Pediat. **21**:198-206 (Aug.) 1942.

(Footnotes continued on next page)

Hyslop [327] reported a case of sporotrichotic meningitis.

Miele reported a case of yeast body meningitis: A 30 year old man had a history dating back to 1933 (eight years), when small white spots were noted in the mouth and on the tongue. Following tonsillectomy in 1934, these spots became red, bleeding and painful. The report of the biopsy specimen was as follows: "Tuberculosis of the submucous area. The surface epithelium is markedly hyperplastic and thickened. Typical tubercles are found below it." Death from chronic meningitis in 1941 was diagnosed as tuberculous meningoencephalitis.

Actinomycosis of the Middle Ear Causing Cerebellar Abscess and Meningitis.—Demianczyk [328] reports a case of primary actinomycosis of the middle ear causing cerebellar abscess and meningitis in a girl 14 years of age. During life a diagnosis of tuberculous meningitis was made. Autopsy revealed actinomycosis of the right cerebellar hemisphere and a circumscribed area of fibrinous pachymeningitis in the region of the right tympanum, with caries of the right tegmen tympani. Serial section showed that the actinomycosis had started at the eustachian tube, had invaded the middle ear spaces and from there had reached the posterior cranial fossa.

Stoddard and Cutler [329] reported 4 cases of meningitis due to Torula histolytica [330] (yeast).

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325. Freeman, W.: Fungus Infections of the Central Nervous System, Ann. Int. Med. **6**:595-607 (Nov.) 1932; Torula Infection of Central Nervous System, J. f. Psychol. u. Neurol. **43**:236-345 (Nov.) 1931.

326. Sporotrichosis is a cutaneous and subcutaneous mycosis (affecting also the mucous membrane of the mouth and the pharynx) caused by mucedines of the genus sporotrichum; three forms (S. beurmanni), a disseminated gummatous lymphangitis (S. schencki) and a form characterized by the presence of multiple abscesses (S. dori).

Parasaccharomyces is a yeastlike fungus, possibly identical with Monilia, found in the intestinal contents; there are several strains or groups designated by letters of the alphabet—A. B, C and so on.

327. Hyslop, G. E.; Neal, J. B.; Kraus, W. M., and Hillman, O.: A Case of Spirotrichosis Meningitis, Am. J. M. Sc. **172**:726-740 (Nov.) 1926.

328. Demianczyk, E.: Primary Actinomycosis of the Middle Ear, Polski przegl. otol. **14**:292, 1938; abstracted, Kopetzky, S. J.: Purulent Otitis Media, Mastoiditis, Sinus Thrombosis and Suppuration of the Petrous Pyramid, Arch. Otolaryng. **32**:962-993 (Nov.) 1940.

329. Stoddard, J. L., and Cutler, E. C.: Torula Infection in Man, Monograph 6, Rockefeller Institute of Medical Research, 1916.

330. Torula (Latin, torulus, diminutive of torus, a swelling). Formerly the term indicated a Genus of budding fungi; now it designates the globular forms of these micro-organisms, such as are frequently assumed by wild yeasts.

Fruit Mold Infection of the Mouth the Cause of Meningitis Mistaken During Life for Tuberculous Meningitis (Miale [331]).—Although the fruit mold "Candida (Monilia [332]) not infrequently attacks . . . the skin, the mucous membranes and the respiratory tract, involvement of the central nervous system is extremely rare." Miale's search revealed only a single previously reported case (Smith and Sano [333]), in which the fungus was identified as Monilia albicans.

In September 1936 (in another hospital) examination revealed a lesion of the mouth, described as "a chronic granulating process involving the buccal surfaces of the mouth, the inner surfaces of the lips and the surfaces of the hard palate, soft palate, uvula, anterior pillars and epiglottis." A tuberculin test was positive. The patient was given a course of generalized treatment with ultraviolet rays.

In February 1937 he stated that one month after the start of the ultraviolet ray treatment he noticed spots and blurring of vision in the right eye, followed rapidly by severe pain and redness of the eye.

The clinical impressions were: panophthalmitis on the right, probably tuberculous; tuberculosis of the mouth.

The right eye was enucleated. Sections showed "an acute and chronic granulomatous lesion. . . . Acid-fast stains of the sections were negative for tubercle bacilli." A week later a biopsy specimen taken from the inner surface of the upper lip showed "nonspecific granuloma."

The patient now complained of hoarseness. The epiglottis showed the same type of lesions as the mouth. The arytenoids and ventricular bands were swollen and slightly red. The impression was that the lesions were probably tuberculous.

For four and a half years (March 1937 to September 1941) the condition remained unchanged.

In November 1941 the patient was observed to be lethargic; for the previous two months he had suffered from severe frontal headaches. His temperature was 100.8 F. He was markedly emaciated. The lower lip had a deeply ulcerated surface. All surfaces of the mouth were covered with gray exudate. The left pupil was fixed. There was choking of the left optic disk. Deep reflexes were absent.

Spinal puncture showed the cerebrospinal fluid under a pressure of 250 mm. of water; the fluid contained 117 cells per cubic millimeter, mostly mononuclears; the protein content was 195 mg. per hundred cubic centimeters. The Pandy test was positive. Six days later the pressure was 400 mm. and cultures of the fluid were negative.

The patient died December 19, after a terminal illness of eighty-three days.

Diagnosis: "Questionable tuberculous meningoencephalitis."

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331. Miale, J. B.: Candida Albicans Infection Confused with Tuberculosis, Arch. Path. **35**:427-437 (March) 1943.

332. Monilia (mo-nil'-i-ah) (Latin, monile, necklace) parasaccharomyces (?), a genus of molds or fungi, fruit molds, having alternating swellings and contractions like a string of beads.

Candicans (Latin, candicare, to be whitish), one of the corpora albicantia, a whitish beaded mass.

333. Smith, L. W., and Sano, M. E.: Monilias with Meningeal Involvement, J. Infect. Dis. **53**: 187-196 (Sept.-Oct.) 1933.

The Brain.—In the pia-arachnoid of the tip of the left parietal lobe there was a finely granular and grayish area consisting of many minute, slightly opaque, glistening nodules. There were also a few small sandy nodules over the right parietal lobe. These small tubercle-like structures were distributed about the pial vessels.

The base of the brain presented a thick, grayish yellow exudate over the pons and peduncles, extending into the fissures between the temporal and frontal lobes. In this exudate were a few small raised tubercle-like nodules.

The ependymal surface of the lateral ventricles was covered with thick, irregular nodular masses. The ependymal surface of the third ventricle was covered with the same kind of granular translucent exudate.

Histologic Studies.—Mouth and tongue sections of the tongue and of the larynx showed granulomatous lesions, with ulceration of the epithelium, marked round cell infiltration, tubercle formation and the presence of many epithelioid cells and giant cells. A few mycelial threads were identified.

The Gram stain brought out mycelial threads and blastospores in the ulcerated areas and in the centers of the tubercles.

Specimens taken from the mouth on Feb. 4, 1937 when treated with the Gram stain revealed typical fungous elements in the deep tissues and in the areas of caseation.

Basilar Meninges: These presented a thick exudate of lymphocytes, with scattered plasma cells, monocytes and large phagocytic cells.

"The third and fourth ventricles were almpst completely occluded by masses of mycelia."

Vascular System of the Brain: There was perivascular infiltration of the smaller vessels in the brain substance; the cells were all mononuclears. The lumen of the superior cerebellar artery was markedly narrowed by thickening and proliferation of the intima.

Right Eye: Sections of the right eye which had been removed five years previously were restudied. In the exudate and necrotic tissue obliterating the posterior chamber and the vitreous, there was a large aggregate of typical mycelia.

Isolation and Identification of the Fungus.—The Sabouraud agar plates showed pure colonies. Smear preparations from young colonies showed gram-positive blastospores and few mycelia. The spores were gram positive, were about 4 or 5 microns in diameter and had thin, doubly refractile capsules.

Dr. N. F. Conant identified the fungus as Candida albicans.

Autopsy Diagnosis.—Chronic stomatitis, glossitis and laryngitis due to Candida (Monilia) albicans; meningitis and ependymitis due to C. albicans; granulomatous endarteritis of the superior cerebellar artery.

Comment (Miale).—"The cells in the spinal fluid were described as mononuclear cells, and it is possible that some of them may have been yeast cells. In the fresh state, and in the absence of a suspicion of any fungus, yeast cells may easily be mistaken for small lymphocytes if no attention is paid to the distinctive doubly refractile capsule."

Candida infections of the mouth are common in children and in old people with chronic debilitating diseases. Their importance is that when they occur in the older age group they may be mistaken for tuberculosis, as in this case.

Giant cells are numerous, probably more numerous than in tuberculosis. Candida spores are difficult to identify, but some of the other fungi, such as Coccidiodes and Blastomyces, are more easily recognized.

Classification of Pathogenic Fungi.—Miale followed Dr. Conant's advice in calling this organism Candida albicans. At a meeting of medical mycologists at the Third International Congress for Microbiology, in September 1939, it was agreed to substitute the generic name of Candida for Monilia.

Soluseptasine (M. & B. 137) Injected into Cerebrospinal Fluid System in "Overflow" Meningeal Infections.

In Hutchinson's [334] experience Soluseptasine as a sulfonanide derivative may be administered intrathecally.

Hutchinson states: "If a sulphonamide derivative could be found of such low toxicity and low irritant properties that it could be introduced with impunity directly into the cerebrospinal fluid, its immediate availability in full concentration right at the seat of infection would enhance its prospects of successfully combating that infection; even though its actual bactericidal properties be less than those of other members of the group, which have to run the gauntlet . . . of the choroid plexus . . ."

"Attempts to introduce sulphonamides intrathecally have . . . not been very encouraging, mainly owing to the irritant properties of the particular derivatives available, . . . resulting in [*a*] hyper-secretion of cerebrospinal fluid and [*b*] excessive local production of fibrin coagulum."

The intrathecal administration of sodium sulfapyridine has been "followed on occasions by convulsions and death."

Hutchinson reports a case in which meningitis due to the hemolytic streptococcus was treated by injecting Soluseptasine directly into the cisterna magna under careful manometric control of the cerebrospinal pressure. The patient was apparently extremely intolerant of both sulfanilamide and sodium sulfapyridine.

"Soluseptasine (M. & B. 137) is a crystalline powder of formula Disodium-p (γ-phenyl-propyl-amino) benzene sulphonamide-a-γ-disulphonate. It is manufactured by Messrs. May & Baker, of Dagenham [England], and it is put up in 5 and 10 per cent solutions."

Hutchinson's Case.—A youth aged 15½ had "chronic mastoiditis with attic cholesteatoma."

February 28: Modified radical mastoidectomy on the right side. Dura exposed. Roof of middle ear cleft eroded.

March 3 to 7: Sulfanilamide by mouth.

March 7: No signs of intolerance to sulfanilamide apart from intense cyanosis. Use of this medicament discontinued.

March 11: Sudden severe headache.

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334. Hutchinson, C. A.: Otogenous Meningitis: Intrathecal Administration of Sulphonamide, J. Laryng. & Otol. **56**:377-386 (Nov.) 1941.

March 17: Temperature 103 F.; of definitely "swinging" character. Administration of sulfanilamide resumed.

March 19: Intense cyanosis, vomiting and severe headache. In spite of extreme cyanosis use of sulfanilamide continued.

March 22: Temperature 101 F. Extreme restlessness. Early papilledema, small retinal hemorrhages, nystagmus on looking to right (side of the otitis). Kernig sign. Lumbar puncture: fluid turbid, blood stained, with fibrin coagulum.

Cerebrospinal fluid specimen: Films: gram-positive cocci in pairs and short chains, 3 plus. Cultures: Streptococcus haemolyticus in pure culture.

Impression: "Either petrositis or a cerebellar abscess had leaked into the subarachnoid space."

Sodium sulfapyridine substituted for sulfanilamide by mouth. Four tablets every four hours for two doses, then two tablets every four hours.

March 23: Exploration through Trautmann's triangle. On incision of dura about 2 ounces (59 cc.) of turbid, blood-stained fluid escaped from a shut-off area between the cerebellum and the posterior surface of the petrous pyramid, extending as far as the internal auditory meatus toward the petrous tip. The fluid appeared to be derived from a closed area to which infection had not penetrated.

Report on fluid from within dura: sugar, 67 mg. per hundred cubic centimeters; no bacteria in film or cultures.

Treatment with sodium sulfapyridine: Two dextrose-saline solution enemas, each containing two tablets of sodium sulfapyridine, three hours apart. Two tablets of sulfapyridine an hour apart, followed by 2 tablets every four hours.

March 24: Cerebrospinal fluid—sugar, 67 mg. per hundred cubic centimeters; no bacteria in films or cultures.

March 25: Daily lumbar puncture to reduce pressure. Fluid very turbid, yet sterile on culture; cells, 5,910 per cubic millimeter.

March 26: "Scanty nonhemolytic streptococci on culture." Five per cent Soluseptasine intrathecally and sodium sulfapyridine by mouth.

Cerebrospinal fluid specimen: "On culture a few colonies of streptococci . . . They were *completely inert (non-hæmolytic)* on blood, and the colonies mucoid." "This is most likely a variant of the original strain under the influence of M. & B. 693" [sodium sulfapyridine].

March 27. Five per cent Soluseptasine intrathecally. Cerebrospinal fluid clear and sterile.

March 28: Lumbar puncture, with 20 cc. of 10 per cent Soluseptasine being given intrathecally. Cerebrospinal fluid clear and sterile.

March 29: Patient extremely cyanosed; vomited twice. Oral administration of sodium sulfapyridine discontinued. Pressure reduced from 285 to 90 mm. by lumbar puncture, with Soluseptasine being injected as before.

March 30: Pressure reduced from 300 to 90 mm. by lumbar puncture, and 15 cc. of 10 per cent solution introduced.

March 31, April 1 and 2: Daily lumbar puncture, reducing pressure from 300 to 90 mm., and 20 cc. of 10 per cent Soluseptasine introduced. Fibrin plugs obstructed the needle. In afternoon sodium sulfapyridine again given by mouth, two tablets every four hours.

April 3: Temperature 100 F. Patient vomited. *Operation:* Cerebellum was thoroughly explored for abscess; no trace of one could be found. Cisterna magna punctured, pressure reduced from 300 to 90 mm., and 20 cc. of Soluseptasine introduced into the cisterna directly. Sodium sulfapyridine given by mouth, two tablets every four hours.

April 4: Marked improvement. Cisterna punctured, with patient under local anesthesia, and 15 cc. of 10 per cent Soluseptasine introduced intracisternally. Sulfapyridine given by mouth as before.

April 5: Cisterna punctured, with patient under local anesthesia; pressure reduced from 230 to 100 mm. and 10 cc. of 10 per cent Soluseptasine introduced. Sodium sulfapyridine therapy continued.

April 6: Temperature normal. Sodium sulfapyridine, two tablets every four hours.

April 7 to 9: Soluseptasine therapy discontinued. Sodium sulfapyridine given as before. Temperature normal, headache gone.

April 11: Lumbar puncture: cerebral fluid clear, with a small fibrin coagulum, and sterile on culture.

April 12 to 17: Sodium sulfapyridine, one tablet every four hours.

April 18: Last day of sodium sulfapyridine therapy. Recovery complete.

Comment (W. P. E.).—I believe that Hutchinson's case was one of what I have designated as "overflow meningitis from a closed empyema of the saccus endolymphaticus." It is a clinical entity. It has been repeatedly encountered operatively during unlocking of the petrous pyramid. In my opinion [335] it was the drainage of the empyemic area that was the chief cause of the patient's recovery; the residual process being controlled by (*a*) lumbar puncture and (*b*) the use of a sulfonamide compound.

Staphylococcus Aureus Meningitis of Otitic Origin Cured by Intramuscular and Intravenous Injections of Penicillin, without Operation (McCollum [336]).

McCollum's case [336] of staphylococcic meningitis secondary to acute suppurative otitis media was without any demonstrable involvement of the mastoid process. The route by which the infection advanced into the subarachnoid space was not determined.

Large doses of penicillin administered simultaneously by intrathecal, intravenous and intramuscular routes brought about a complete recovery. No beneficial effect was noted from the initial intravenous and intramuscular administration of 100,000 units of penicillin.

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335. Eagleton, W. P., in discussion on Cunning, D. S.: Treatment of Otitic Meningitis, Arch. Otolaryng. **30**:950-972 (Dec.) 1939; in discussion on Converse, J. M.: Recurrence of Otitic Infections Due to Beta-Hemolytic Streptococcus Following Inadequate Sulfanilamide Therapy, Tr. Sect. Laryng., Otol. & Rhin., A. M. A., 1939, pp. 145-146; J. A. M. A. **113**:1383-1387 (Oct. 7) 1939; in discussion on Symposium: What Is Justifiable to Do in Otitic Meningitis? Tr. Am. Otol. Soc. **28**:73-76, 1938; Intradural Conditions in Relation to Rhinology and Otology: Critical Survey of Recent Literature, Arch. Otolaryng. **32**:54-120 (July); 256-298 (Aug.) 1940.

336. McCollum, W. D.: Cure of Staphylococcic Meningitis of Otitic Origin with Penicillin, Arch. Otolaryng. **40**:514-515 (Dec.) 1944.

Only 15,000 units of penicillin was administered intrathecally, and McCollum does not believe this amount could have been reduced with safety. However, the amounts given intravenously and intramuscularly, totaling 2,285,000 units, may eventually be proved to have been more than adequate. However, penicillin was administered on the the second day. No untoward effects were noted from its use.

Private J. U. was admitted to the hospital, Jan. 22, 1944, because of headache, fever and general malaise of twenty-four hours' duration. Five days prior to admission he had earache on the right side, soon after which he noted a slight discharge. The discharge stopped within twenty-four hours. There were no further symptoms until twenty-four hours before he was hospitalized.

January 23 he complained of increasingly severe headache, nausea, and stiffness of the neck. He vomited. Examination of the right ear showed a small perforation of the lower middle part of Shrapnell's membrane. Impression: Acute suppurative otitis media and meningitis.

A smear of material from the ear showed gram-positive cocci.

The spinal fluid grossly was cloudy. The patient was given 6 Gm. of sulfadiazine immediately and 2 Gm. thereafter at four hour intervals.

In the early afternoon the patient appeared more drowsy.

Myringotomy was performed. Smear revealed gram-positive cocci, later identified as Staph. aureus of a nonhemolytic type.

The spinal fluid on smear revealed gram-positive cocci (later identified as Staph. aureus). The cell count showed 5,600 white cells per cubic millimeter (66 per cent polymorphonuclears and 34 per cent lymphocytes). Globulin was markedly increased. The total protein amounted to 67 mg. per hundred cubic centimeters.

Thirty hours after admission his temperature was 104 F., Brudzinski's and Kernig's signs were present, and knee jerks were absent.

In view of the fact that the infective agent was a gram-positive organism, thought to be Staph. aureus, it was realized that sulfadiazine would be inadequate. Penicillin was indicated and its use strongly desired. The evening of January 23 (twenty-eight hours after his admission) treatment with penicillin was initiated. During the night the patient received 10,000 units intramuscularly and 10,000 units intravenously every two hours for a total of 100,000 units.

January 24 sulfadiazine therapy was discontinued. Cloudy spinal fluid was obtained under a pressure of 250 mm. (water manometer). His temperature was 105 F. It was evident that the penicillin would have to be increased and the intramuscular and intravenous injections complemented by intrathecal injection.

The following schedule was initiated: A spinal tap was done daily, with removal of 15 cc. or more of spinal fluid. Then 10 cc. of saline solution containing 5,000 units of penicillin was injected into the spinal canal. A continuous intravenous drip of a 5 per cent solution of dextrose in distilled water was arranged, and 1 cc. of penicillin (5,000 units per cubic centimeter) was injected into the tubing of the intravenous drip setup every half-hour. Every three hours 5 cc. of penicillin (25,000 units) was injected intramuscularly. Plasma and blood transfusions were to be given as indicated.

January 25 the maximum temperature was 101.5 F.; January 26, 100.5 F.; January 28, 99 F.

ADVANCES IN INTRACRANIAL TECHNIC

Fibrin Foam as a Hemostatic Agent in Cranial Surgery (Woodhall [337]).

Ingraham and Bailey [338] introduced fibrin foam [339] as a hemostatic agent into neurologic surgery in 1944—a great technical advance. Up to this time the silver clip, the electrocautery and cotton patties soaked in warm saline solution or muscle stamps had been used.

Fibrin foam has been used as a hemostatic agent in 226 neurosurgical operations. In each instance the desired hemostatic effect was secured promptly. No clinical untoward reactions that could have been attributed to the use of fibrin foam have been observed.

CHEMOTHERAPY

Differences in Antibacterial Action of Sulfonamide Compounds and Penicillin (MacLeod and Stone [340]).

"*Summary.*—1. The sulfonamide drugs are . . . bacteriostatic and require for . . . effective action the participation of specific antibody and an active phagocytic system . . .

"2. Penicillin exerts a direct bactericidal effect . . . and hence its therapeutic efficacy is not as dependent on the development of specific immunity as in the case of the sulfonamides. . . .

"3. Failure of sulfonamide therapy in localized purulent infections, even though [the drugs are] introduced directly into them, is due in all likelihood to a number of factors: [*a*] the presence of sulfonamide inhibitors, . . . [*b*] an unfavorable p_H, [*c*] development of sulfonamide fastness, and [*d*] the absence from the lesions of specific antibody and functional phagocytes.

"4. . . . the immediate antibacterial effect of penicillin, as contrasted with the lag phase characteristic of the action of the sulfonamides, may be of importance . . ."

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337. Woodhall, B.: Fibrin Foam as a Hemostatic Agent in Rehabilitation Neurosurgery, J. A. M. A. **126**:469-471 (Oct. 21) 1944.

338. Ingraham, F. D., and Bailey, O. T.: The Use of Products Prepared from Human Fibrinogen and Human Thrombin in Neurosurgery: Fibrin Foams as Hemostatic Agents; Fibrin Films in Repair of Dural Defects and in Prevention of Meningocerebral Adhesions, J. Neurosurg. **1**:23-39 (Jan.) 1944. Ingraham, F. D.; Bailey, O. T., and Nulsen, F. E.: Studies on Fibrin Foam as a Hemostatic Agent in Neurosurgery, with Special Reference to Its Comparison with Muscle, ibid. **1**:171-181 (May) 1944.

339. Bering, E. A., Jr.: Chemical, Clinical and Immunological Studies on the Products of Human Plasma Fractionation: XXII. The Development of Fibrin Foam as a Hemostatic Agent for Use in Conjunction with Human Thrombin, J. Clin. Investigation, to be published.

340. MacLeod, C. M., and Stone, E. R.: Differences in the Nature of Antibacterial Action of the Sulfonamides and Penicillin and Their Relation to Therapy, Bull. New York Acad. Med. **21**:375-388 (July) 1945.

Penicillinase.— . . . "certain organisms, both gram positive and negative, may elaborate an enzyme, penicillinase, which destroys penicillin. The importance of this enzyme as a cause of failure of penicillin therapy has not been adequately assessed."

Drug Fastness and Resistance.—"Sulfonamide fastness may be an inherent property of all members of a species or genus of bacteria. . . . One may speak of such fastness as [*a*] natural in contrast to [*b*] the acquired fastness . . .

. . . Acquired fastness is a commonplace finding during sulfonamide therapy, particularly with staphylococci and, to a lesser extent, pneumococci. Staphylococci possess the ability to become fast fairly rapidly not only to the sulfonamides, but also to . . . penicillin. For this reason, in addition to the circumscribed, walled-off lesion which they cause characteristically, staphylococcal infections present a somewhat unique problem in chemotherapy" (MacLeod and Stone [340]).

Tillett and co-workers [341] have shown that empyema fluid from patients does not always contain "sulfonamide inhibitor," yet local therapy with sulfonamide drugs is unsuccessful. The success of penicillin under these circumstances may be due not so much to the absence of penicillin inhibitor as to the bactericidal properties of the compound.

Plasma Binding of Different Sulfonamide Drugs, Forming a Nondialyzable Fraction in Cerebrospinal Fluid.

The concentration of any sulfonamide compound is somewhat lower in the cerebrospinal fluid than in the blood. This is in part due to the tendency of the sulfonamide compound to combine with plasma proteins, forming a nondialyzable fraction, and in part to the mechanism of formation of the cerebrospinal fluid. The extent of the plasma binding is: sulfadiazine, 20 per cent; sulfapyridine, 30 per cent; sulfamerazine, 40 per cent, and sulfathiazole, 60 per cent.[342]

Hemolytic Streptococcus Bacteremia of Sphenoiditic Origin, Probably Caused by Exacerbation of the Sphenoidal Suppuration Following Administration of a General Anesthetic.

Goldman [343] illustrates the effectiveness of chemotherapy in preventing complications arising from suppuration of the sphenoid sinus.

A man aged 30 underwent an operation on the knee under general anesthesia induced with gas, oxygen and ether. Two days later he had right supraorbital headache and a nasal discharge. Six days later the headache shifted to the occiput

341. Tillett, W. S.; Cambier, M. J., and McCormack, J. E.: Treatment of Lobar Pneumonia and Pneumococcal Empyema with Penicillin, Bull. New York Acad. Med. **20**:142-178 (March) 1944.

342. The Sulfonamides, editorial, J. A. M. A. **124**:646 (March 4) 1944.

343. Goldman, I. B.: Hemolytic Streptococcic Bacteremia of Sphenoidal Origin, Laryngoscope **53**:499-501 (July) 1943.

and became unbearable. When he was admitted to the hospital two days later, his temperature was 99 F. and he was vomiting. He had a chill, and his temperature rose to 104.2 F.

Blood culture showed innumerable colonies of hemolytic streptococci.

Right sphenoethmoidectomy showed the mucous membrane gangrenous and covered with pus but no disease of bone.

Culture of material from the sphenoid sinus yielded hemolytic streptococci.

The headache disappeared dramatically, but the patient still had occasional slight pains in the right temporal region. Sulfanilamide was given for a week, a total dose of 41 Gm.

Comment (Goldman).—The symptoms followed so closely on the administration of a general anesthetic that a causal relationship may have existed. Cyclopropane and ether cause nasal irritation and hypersecretion, and may thus contribute to a flare-up of a latent infection of the sinuses, especially of the sphenoid sinuses, because of their dependent position when an anesthetic is administered.

Goldman believes it conceivable that the anesthesia induced with gas, oxygen and ether at the time the knee was operated on contributed to the development of the disease in the sphenoid sinus.

Case of Meningitis After Appendectomy.—Goldman refers to a case of Kepes' in which in a woman 30 years of age fever and headache suddenly developed several days after she had undergone appendectomy. When meningitis developed, mastoidectomy was performed. No pathologic changes were found. At autopsy marked suppuration of the sphenoid sinus was observed, with pus and necrosis of its lateral wall.

Pathologic Data in Fourteen Cases of Renal Insufficiency Due to Intoxication with Sulfonamide Compounds (Murphy and associates [344]).

Thirteen of the 14 patients died and were studied post mortem.

Quantity of Drug.—The quantity of the sulfonamide compound administered and the level maintained in the blood appeared to be unimportant in producing the renal damage. As much as 41 Gm. and as little as 0.6 Gm. were responsible for fatal renal injury.

Mechanical Obstruction from Crystals.—In a few cases deposits of crystals of the drugs in the urinary tract caused some degree of mechanical obstruction associated with the nephrotoxic lesion; but this was not the rule, as in most of the cases reported the nephrotoxic lesion was independent of mechanical blocking.[345]

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344. Murphy, F. D.; Kuzma, J. F.; Polley, T. Z., and Grill, J.: Clinicopathologic Studies of Renal Damage Due to Sulfonamide Compounds: A Report of Fourteen Cases, Arch. Int. Med. **73**:433-443 (June) 1944.

345. Prien, E. L.; Crabtree, E. G., and Frondel, C.: Mechanism of Urinary Tract Obstruction in Sulfathiazole Therapy: Identification of Crystals in Tissue by Polarized Light, J. Urol. **46**:1020-1032 (Nov.) 1941. Lowenberg, S. A.; Sloane, N. G., and Chodoff, P.: Sulfathiazole Urinary Calculi in the Kidneys, Ureters and Bladder in the Absence of Marked Urinary Changes Following Sulfathiazole Therapy, J. A. M. A. **115**:2069-2071 (Dec. 14) 1940.

Comment (W. P. E.).—Of the 14 patients, all but 1 were suffering from diseases that were the immediate cause of death; so Murphy's statistics are not applicable to cases in which sulfonamide drugs are given for intracranial suppuration.

At the Newark Eye and Ear Infirmary we have had 2 cases of urinary suppression due to mechanical obstruction from (anacetylated) crystals of a sulfonamide compound given for an intracranial suppuration of otitic origin. The condition was relieved by irrigation of the ureters.

Influence of Hydrogen Ion Concentration.—According to Schmelkes,[346] the effectiveness of the sulfonamide compounds is greatly influenced by the hydrogen ion concentration of their environment. The presence of some polar compounds, such as urea and asparagine, increases the activity of the sulfonamide compounds. Oxidizing agents, such as chloroazodin, have a similar effect.

Experimental Effect of Certain Sulfonamide Compounds on the Electric Activity of the Cerebral Cortex.—"The local application of sulfonamides to cranial injuries has become . . . widespread . . . , particularly in military surgery. Recently reports by Watt and Alexander[347] . . . and Pilcher and his co-workers[348] . . . indicated that sulfathiazole in particular should not be allowed to come in contact with the cerebral cortex because of the danger of generalized convulsions. Sulfadiazine and sulfapyridine did not appear to possess this disadvantage. . . ." Brenner and Cohen[349] have undertaken "a series of experiments designed to determine the effect of local applications of various sulfonamides on the electrical activity of the cortex."

Their conclusions are:

[1.] "Neither sulfanilamide nor its sodium salt in concentrations up to 20 per cent had any significant effect on the electrical activity of the cortex of lightly anesthetized cats.

[2.] "Solutions of the sodium salts of sulfathiazole, sulfapyridine or sulfadiazine produced striking changes in the electrical records . . . interpreted as evidence" . . . of a convulsant action on the cerebral cortex of the cat. [3.] Sulfathiazole powder produced the same electrical changes and on one occasion was accompanied by a focal seizure. [4.] Sulfapyridine powder produced increased electrical activity of a less striking kind. [5.] Sulfadiazine powder produced no significant change in electrical activity."

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346. Schmelkes, F. C.: Chemical Considerations Governing the Local Chemotherapy of Wound Infections, Surg., Gynec. & Obst. **77**:69-73 (July) 1943.

347. Watt, A. C., and Alexander, G. L.: Epilepsy Following Application of Sulfathiazole Near Brain, Lancet **1**:493-495 (April 25) 1942.

348. Pilcher, C.; Angelucci, R., and Meacham, W. F.: Convulsions Produced by Intracranial Implantation of Sulfathiazole: Preliminary Report, J. A. M. A. **119**:927 (July 18) 1942.

349. Brenner, C., and Cohen, S.: Effect of Certain Sulfonamides on the Electrical Activity of the Cerebral Cortex, J. A. M. A. **123**:948-950 (Dec. 11) 1943.

Sulfanilamide the Safest.—"As far as irritant or possible convulsant action on the cortex is concerned sulfanilamide is the safest of these four drugs for local intracranial application where there is a possibility of contact with the cerebral cortex."

Epileptogenic Effect of Sulfathiazole Demonstrated in Rabbits, Cats and Human Beings.—Meacham and his associates [350] studied the pathologic effects of sulfanilamide, sulfathiazole and sulfadiazine implanted intracranially by various methods and in various amounts on the brain and its coverings in 115 experiments on dogs. They observed (1) that sulfathiazole when placed on the intact cerebral cortex produced convulsions.

"The production of convulsions by placement of sulfathiazole on the cortex" indicates "that these seizures may be produced when the drug is placed extradurally, provided a very small opening in the dura exists."

(2) "The violence and the fatal outcome of the seizures which followed the cisternal injection of suspensions of microcrystalline sulfathiazole" are possibly due to a "direct toxic effect on the medulla."

(3) "Convulsions were never produced when sulfathiazole was placed in an excavation in the cerebral hemisphere. Seemingly, the effect of the drug must be exerted on the intact cortex in order to induce convulsions."

(4) *Sulfanilamide and Sulfadiazine Rarely Produce Convulsions.*—"That convulsions were not produced in the experiments with kaolin, and rarely with sulfanilamide or sulfadiazine, indicates that the effect of sulfathiazole is specific."

(5) *Pathologic Effects.*—These were (*a*) immediate acute pachymeningitis and leptomeningitis, with corresponding subacute or chronic inflammation in the later stages, (*b*) pronounced fibroplasia in the dura, (*c*) conspicuous gliosis in the cortex and (*d*) varying degrees of neuronal degeneration, proliferation of oligodendrogliocytes and metamorphosis of microglia cells.

(6) All reactions were least extensive when sulfanilamide was employed.

Their conclusions are that these experiments do not indicate that the effects of sulfanilamide and sulfadiazine are sufficiently harmful to contraindicate the critical use of these drugs in the therapy of intracranial infections. They suggest that sulfathiazole should never be employed in a cranial wound in which there is an opening in the dura.

Cases of Epileptic Attack Following Application of Sulfathiazole on Cerebral Cortex.—In the case reported by Naffziger [351] in which sulfathiazole was placed in a frontal craniotomy wound after suture of the dura, the patient went into status epilepticus, which lasted many hours. Watt and Alexander [347] reported a similar case.

PENICILLIN

The history of penicillin is essentially the story of three distinct developments: [352] "The first was Fleming's discovery in 1929 [353]; the second

350. Meacham, W. F.; Angelucci, R.; Benz, E., and Pilcher, C.: Chemotherapy of Intracranial Infections: II. Clinical and Pathologic Effects of Intracranial Introduction of Sulfanilamide, Sulfathiazole and Sulfadiazine in Normal Dogs, Arch. Neurol. & Psychiat. **50**:633-651 (Dec.) 1943.

351. Naffziger, H. A.: Personal communication to the authors.[350]

(Footnotes continued on next page)

was that of Florey and his colleagues,[354] who showed how to obtain penicillin in a relatively pure form and who demonstrated its clinical use"; and the third was this country's attainment of large scale production of the drug.

Pasteur and Joubert's Early Discovery.—In 1877 Pasteur and Joubert[354] had observed that cultures of anthrax ceased to grow when contaminated with air bacteria; this, Florey[355] believes, was the first evidence that a substance produced by one organism is capable of arresting the growth of another.

Pasteur proposed that in the soil there must exist organisms of various characteristics, capable of lysing and destroying the countless billions of pathogens excreted by man and other animals.[356]

History of Penicillin.—In 1929 Alexander Fleming made the observation that a plate containing Staphylococcus colonies became transparent, indicative of lysing organisms, owing to its contamination with the mold Penicillium notatum.[356] Fleming called the principle in certain strains of P. notatum "penicillin."

Chemical Properties.—Penicillin is a by-product of the metabolism of the growth of the mold Penicillium; it goes into solution in the medium. This by-product is a complex acid. Fleming[357] found that the principle was water soluble, not affected by gentle heat and stable in neutral or alkaline solutions.

Only two papers appeared on penicillin during eleven years; one by Clutterbuck, Lovel and Raistrick,[358] in 1932.

The by-product was reinvestigated by Florey, Chain and their co-workers nine years after its original discovery by Fleming[359] in 1929. There was delay in recording their results because Professor Florey did not want to detract from the honor due Professor Fleming. Interest in it was revived, growing out of

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352. Penicillin Production, editorial, Brit. M. J. **2**:186 (Aug. 5) 1944. Fleming, A.: The Discovery of Penicillin, Brit. M. Bull. **2**:4-5 (Jan.) 1944; cited in History of Penicillin, editorial, J. A. M. A. **126**:170-172 (Sept. 16) 1944.

353. Fleming, A.: On Antibacterial Action of Cultures of Pencillium with Special Reference to Their Use in Isolation of B. Influenzae, Brit. J. Exper. Path. **10**:226-236 (June) 1929.

354. Pasteur and Joubert: Chimie physiologique—Charbon et septicemie, Compt. rend, Acad. d. sc. **85**:101-115, 1877.

355. Florey, H. W.; Chain, E.; Gardner, A. D.; Heatley, N. G.; Jennings, M. A.; Orr-Ewing, J., and Sanders, A G: Penicillin as Chemotherapeutic Agent, Lancet **2**:226-228 (Aug 24) 1940. Florey, H. W.: Penicillin: Survey, Brit. M. J. **2**:169-171 (Aug. 5) 1944.

356. The Romance of Penicillin, The Doctor and OD Quart. **54**:1-2 (Dec.) 1944.

357. Fleming, A.: On Specific Antibacterial Properties of Penicillin and Potassium Tellurite, Incorporating Method of Demonstrating Some Bacterial Antagonisms, J. Path. & Bact. **35**:831-849 (Nov.) 1932.

358. Clutterbuck, P. W.; Lovel, R., and Raistrick, H.: The Formation from Glucose by Members of the Penicillium Chrysogenum Series of a Pigment, an Alkali Soluble Protein—the Antibacterial Substance of Fleming, Biochem. J. **26**:1907-1918, 1932.

359. Fleming writes: "I have used penicillin constantly since 1929 for differential culture but its use for practical therapeutic purposes remained in abeyance until the Oxford workers started their investigation" (Brit. M. Bull. **2**:5 [Jan.] 1944).

the investigations of workers in Oxford University: Chain, Florey, Gardner, Jennings, Orr-Ewing and Sanders, who published "Penicillin as a Chemotherapeutic Agent" in August 1940,[360] and isolated penicillin in the form of a brown powder.

Fleming[361] stated that "while hundreds of different molds have been tested so far, none of them have yielded extracts with the combination of high antibacterial activity associated with low toxicity for . . . human beings." The same species of Penicillium from which he extracted the first minute quantity of penicillin in September 1928 is still the species from which penicillin is now obtained in mass production.

He said: "I had no suspicion that I got a clue to the most powerful therapeutic substance yet used to defeat bacterial infections in the human body. But the appearance of the culture plate was such that I thought it should not be neglected. So I made pure cultures from the strange mold and most of the penicillin hitherto produced has been made from descendants of this one colony."

High Grade Ethics of British Scientists in Regard to Pharmaceutic Preparations of General Therapeutic Value.—It was work on an antibiotic agent, lysozyme, discovered by Fleming in 1922, developed by Florey[362] in 1936 and crystallized by Roberts[363] in 1937, that created interest in penicillin at the Sir William Dunn Institute of Pathology.

In the fall of 1937 Falk[364] came to Oxford as a Rhodes scholar to work in Florey's laboratory. To quote Falk: "He [Florey] assigned me my doctorate thesis subject, 'The Actions of Certain Bacteriolytic Principles' and allowed me to choose Dr. Ernest Chain . . . as my supervisor. . . . During the course of this work we began to share Florey's interest in other antibacterials of cellular origin . . . We read Fleming's original 1929 paper on penicillin . . . and found it difficult to understand why the study of penicillin had practically lapsed for nine years. It appeared that this was probably due mainly to the difficulties in purification of the substance and not because the observations had not been confirmed.[354]

"We . . . were able to borrow a strain of the Fleming Penicillium notatum from. . . . Miss Campbell-Renton [in the Sir William Dunn School of Pathology]. She had kept the original Fleming strain going . . . Chain and I (Falk) recultured this strain and tested the antibacterial properties of the medium . . . Professor Florey asked Dr. Norman Heatley to work with Chain on the further development of penicillin. This was in 1938, as I recall. Heatley and Chain, with the active advice of Professor Florey, succeeded in purifying and standardizing penicillin, and by the late spring of 1940 . . . had

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360. Florey and others.[355] Dawson, M. H.; Hobby, G. L.; Meyer, K., and Chaffee, E.: Penicillin as a Chemotherapeutic Agent, J. Clin. Investigation **20**: 434 (July) 1941. Abraham, E. P.; Chain, E.; Fletcher, C. M.; Gardner, A. B.; Heatley, N. G.; Jennings, M. A., and Florey, H. W.: Further Observations on Penicillin, Lancet **2**:177-188 (Aug. 16) 1941. Footnote 356.

361. Fleming, A., in a broadcast from London to the American Pharmaceutical Manufacturers Association, meeting at the Waldorf-Astoria, New York, Dec. 13, 1943.

362. Florey, H.: Relative Amounts of Lysozyme Present in Tissues of Some Mammals, Brit. J. Exper. Path. **114**:251-261 (Aug.) 1930.

363. Roberts, E. A. H.: Preparation and Properties of Purified Egg-White Lysozyme, Quart. J. Exper. Physiol. **27**:89-98 (July) 1937.

364. Falk, L. A.: The History of Penicillin, J. A. M. A. **124**:1219 (April 22) 1944.

produced enough partially purified penicillin for use in animal experiments. . . . The importance of the findings was understood at once, and practically the whole Sir William Dunn Institute of Pathology was turned over to penicillin research, the work being financed mainly by the British Medical Research Council. It is a tribute to the wisdom of British science and to the British people as a whole that all this was accomplished at exactly the period of the greatest peril to their country—when France capitulated and when it appeared possible that the Nazis would invade England itself. . . . Professor Florey's visit to the United States in the summer of 1941 stimulated interest in it here. Commercial production was undertaken, . . . It has been wisely shepherded by the National Research Council and given only to qualified investigators."

The Unit of Penicillin.—The unit of penicillin, designated as the Oxford unit or Florey unit, is that amount of penicillin which when dissolved in 50 cc. of meat extract broth just inhibits the growth of the test strain of Staphylococcus aureus. Penicillin appears to be of low molecular weight.[356]

Penicillin in Intracranial Suppuration.

Keefer and his associates,[365] as the result of their study of 500 cases of infection, state that penicillin has not had much effect in patients with abscess of the brain and complicating meningitis; it may sterilize the spinal fluid. In pneumococcic meningitis with bacteremia the drug is often a bacteriologic success but a clinical failure. In short, penicillin is a very effective, relatively nontoxic anti-infective agent for gram-positive pathogens. In the great bulk of the infections with gram-negative organisms, however, it is of no value; in fact, it fosters the growth of these.

Two patients died following infections of the throat with thrombophlebitis of the deep cervical veins (postanginal sepsis) (Keefer and associates [366]).

"With . . . the intrathecal injection of penicillin, in normal subjects, the substance is slowly absorbed and slowly excreted in the urine following the injection of 5,000 or 10,000 Oxford units," and "in the spinal fluid for at least 31.5 hours after the injection . . . There is some evidence that penicillin is slightly irritating to the normal meninges, and the injection of 10,000 Oxford units into the subarachnoid space may be followed by headache, vomiting, increased intrathecal pressure and pleocytosis in the spinal fluid. . . .

"In patients with meningitis, absorption of penicillin from the intrathecal space is more rapid than in normal subjects, and a greater amount of that injection is excreted in the urine. Penicillin can be detected in the spinal fluid twenty-four hours after its injection" (Keefer and associates [366]).

365. Keefer, C. S.: Penicillin, in Tenth Annual Series of Conference Talks at the Institute of Living, Feb. 9, 1944.

366. Keefer, C. S., and others: Penicillin in the Treatment of Infections: A Report of 500 Cases, J. A. M. A. **122**:1217-1224 (Aug. 28) 1943.

Keefer and his associates have been unable "to detect penicillin in the cerebrospinal fluid after intravenous or intramuscular injection; for this reason it is well . . . to use penicillin both intravenously and intrathecally in the treatment of meningitis."

Intraventricular Injection of Penicillin in the Treatment of Staphylococcic Meningitis Resistant to Sulfadiazine.—In a case reported by McCune and Evans,[367] after the clinical course had reached a standstill under intrathecal administration of penicillin, the drug was injected into the ventricles to insure maximum levels within the brain, and this was not accompanied by untoward effect.

June 12, 1943 the patient was struck by an automobile and rendered unconscious. Roentgenographic films showed a linear fracture in the right frontal bone starting 1 cm. from the midline and extending into the right frontal accessory nasal sinus.

For the following two weeks the patient remained semiconscious, restless and incontinent.

On admission to the hospital June 26 (two weeks after the accident) he was still unconscious. His temperature was 105 F. There was moderate rigidity of the neck, a positive Kernig sign, absence of the abdominal reflexes and positive Babinski and Gordon signs on the right.

Spinal puncture revealed cloudy fluid under an initial pressure of 180 cm. of water; it contained 23,750 leukocytes per cubic millimeter, 90 per cent polymorphonuclears. Cultures showed Staphylococcus aureus. An electroencephalogram showed the dominant rhythm to be slow, but there was evidence of focalization.

Treatment.—Sodium sulfadiazine, 5 Gm., was administered intravenously, followed by 2.5 Gm. every twelve hours for two days.

June 28 (two days later) his temperature was still high, 103.8 F. The cerebrospinal fluid pressure was 210 cm. of water; the cell count was 6,480 leukocytes, 90 per cent polymorphonuclears; a culture of the fluid was positive for Staph. aureus. Consequently, intrathecal injection of penicillin was begun—initial dose 10,000 Florey units. This was followed by 7,500 units intrathecally twice daily for three days, then by 5,000 units twice daily for five days.

Still there was unconsciousness, but his temperature dropped to 101.4 F. The number of leukocytes in the spinal fluid dropped to 2,200 on June 30, and the culture became sterile.

July 5 his temperature rose to 102 F. A needle was passed into the right ventricle, and 8 cc. of slightly turbid colorless fluid was withdrawn, which showed only "minimal bacteriostatic activity in spite of the fact that 7,500 units of penicillin had been introduced by lumbar puncture two hours earlier." Fluid removed from the right ventricle contained 170 leukocytes, 59 per cent of which were polymorphonuclears.

Introduction of Penicillin Solution into Ventricle.—Seventy-five hundred Florey units of penicillin dissolved in 5 cc. of saline solution was introduced into the ventricle.

July 6 (following day) his temperature was 101 F.

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367. McCune, W. S., and Evans, J. M.: Intraventricular Penicillin in the Treatment of Staphylococcic Meningitis, J. A. M. A. **125**:705-706 (July 8) 1944.

July 7 his temperature rose to 103 F. On spinal tap the fluid appeared much clearer and contained only 675 leukocytes, 65 per cent of which were polymorphonuclears. A culture of the fluid remained sterile.

Because of the shortage of penicillin, the injection of it was stopped on July 7 and administration of sodium sulfadiazine begun with an initial intravenous dose of 5 Gm., followed by 2.5 Gm. every twelve hours until July 11. From July 11 to July 18, 4 Gm. of sulfadiazine was given daily by mouth.

After the withdrawal of penicillin and the change to sulfadiazine the spinal fluid cell count rose to 345 cells on July 10 and 665 cells on July 12 but then gradually fell to a count of 17 cells (4 per cent polymorphonuclears) on July 26. A small, old subdural hygroma containing about 14 cc. of clear yellow sterile fluid was evacuated through a right frontal burr hole.

This case shows that [1] "Intraventricular use of penicillin as an adjunct to the intrathecal route of administration is possible without untoward reactions and with good effect. . . . There was evidence of . . . [2] minimal passage of penicillin from the spinal canal into the ventricles in two hours . . . [which] reemphasizes . . . that the normal flow of cerebrospinal fluid may hinder the free passage of therapeutic agents from the spinal canal into the ventricular system. This is especially true . . . when arachnoid adhesions and exudate [of meningitis] partially obstruct the normal spinal fluid pathways."

MacLeod and Stone[368] state: "Lesions produced by staphylococci characteristically localize early and become surrounded by a pyogenic membrane which prevents diffusion of chemotherapeutic agents into them. If therapy has not been begun before walling-off has taken place, it may be necessary to eradicate the local lesions by surgical procedures or else introduce adequate concentrations of penicillin directly. The sulfonamides exert little effect on localized staphylococcal infections, though they may be lifesaving in preventing overwhelming systemic infection. Their failure locally may be attributable to the presence of sulfonamide inhibitors, acid reaction of the pus or absence of specific antibodies and functional phagocytes which appear to be essential for the therapeutic action of these bacteriostatic compounds.

"Factors other than a pyogenic membrane may prevent diffusion of a chemotherapeutic agent into the involved area. Most of the sulfonamide drugs pass readily into the cerebrospinal fluid and hence treatment of meningitis with sulfonamides can be carried out without recourse to intrathecal administration. . . . Penicillin is extremely active against the meningococcus but following intramuscular or intravenous injection, very little of the compound appears in the cerebrospinal fluid. It must therefore be injected intrathecally, as well as by other routes in treating meningitis."

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368. MacLeod and Stone,[340] p. 386.

In Meningitis (Dawson and Hobby [369]).—"The 4 cases of pneumococcic meningitis all responded satisfactorily. In 2 of the 4, however, it was impossible to evaluate the role of penicillin because sulfonamides and antipneumococcus serum also were administered. In the third case the infection persisted in spite of adequate sulfadiazine therapy for twelve days. Penicillin was administered intrathecally, 20,000 units daily for three days, and systemic treatment instituted as well. Within twenty-four hours the temperature returned to normal, the spinal fluid became sterile, and thereafter recovery was uneventful. The fourth case was complicated by the presence of mastoiditis and petrositis, and it was necessary to continue treatment for fifteen days before a satisfactory outcome was obtained. In this case also sulfonamides had proved completely ineffective. In 3 of the 4 cases of pneumococcic meningitis, penicillin was administered intrathecally as well as systemically; in 1 case systemic treatment alone was employed."

In Abscess of the Brain.—"The purified extract is active in very high dilutions and is not inhibited by pus, exudates, tissue cells or para-aminobenzoic acid, and is nontoxic even in large doses" (Crowe and associates [370]).

In Putney's [371] case of cerebellar abscess "infection in the mastoid was controlled by the drug . . . but the signs of cerebellar irritation continued even though the temperature became normal. At operation the pus in the brain abscess was found to be sterile, demonstrating the efficacy of the drug in eliminating the bacteria, but healing was not obtained until surgical drainage had been instituted."

"Case 10.—*Acute mastoiditis with cerebellar abscess:*

A 30 year old sergeant was admitted to the hospital with pain over the left side of the head, stiffness of the neck and a purulent discharge from the left ear. The spinal fluid contained 4,750 cells, 93 per cent of which were polymorphonuclears, but no organisms could be demonstrated by smear or culture. The day after admission the patient was started on treatment with penicillin, receiving 25,000 units intramuscularly every three hours, and the following day a simple mastoidectomy was performed. At operation the lateral sinus was explored and found to be patent, but some pus was encountered around and below the upper knee. Culture revealed beta hemolytic streptococci. Penicillin was given for twelve days, the patient receiving a total of 1,755,000 units.

"While the patient was under therapy, the fever disappeared, and the cell count of the spinal fluid dropped to 51, but weakness, dizziness, vomiting and nystagmus began. These symptoms together with severe headaches on the left

369. Dawson, M. H., and Hobby, G. L.: The Clinical Use of Penicillin: Observations in One Hundred Cases, J. A. M. A. **124**:611-622 (March 4) 1944.

370. Crowe, S. J.; Fisher, A. M.; Ward, A. T., Jr., and Foley, M. K.: Penicillin and Tyrothricin in Otolaryngology, Based on a Bacteriological and Clinical Study of 118 Patients, Ann. Otol., Rhin. & Laryng. **52**:541-572 (Sept.) 1943.

371. Putney, F. J.: Penicillin in Mastoiditis and Its Complications, Arch. Otolaryng. **41**:247-251 (April) 1945.

side and signs of cerebellar involvement continued until the mastoid cavity was reopened eighteen days after the original operation. At the second operation a needle was introduced beneath the upper knee of the sigmoid sinus into the anterior portion of the cerebellum, and approximately 7 cc. of sterile pus was evacuated. The opening into the abscess cavity was enlarged, and a rubber drainage tube was inserted after the abscess was irrigated with penicillin. The wound was closed, and instillations of penicillin directly into the cerebellar abscess was carried out every three hours for the next two days. The rubber tube was then removed, and the patient continued to improve, all signs and symptoms disappearing."

"Ten cases are reported which described brain (cerebellar) abscess, epidural abscess, mastoiditis, thrombosis of the lateral sinus, petrositis and meningitis. . . . sulfonamide compounds were administered in 8 of the 10 cases without clearing the infection, but prompt response was obtained from treatment with penicillin." Judging from the results obtained, Putney feels that "penicillin in combination with adequate surgical intervention offers the most effective means of combating the serious and life-endangering otologic complications."

Intrathecal Injections of Penicillin in Abscess of the Brain and Meningitis.—Rammelkamp and Keefer [372] treated 6 patients by intrathecal injection of penicillin, including 2 with abscess of the brain and meningitis and 2 with meningitis. In 2 patients who died, penicillin was demonstrated in the cerebrospinal fluid removed from the third ventricle and from the cisterna magna. They suggested an initial dose of not more than 10,000 Florey units, followed by doses of 5,000 units every twenty to twenty-four hours. There were no reactions to the intrathecally injected penicillin except as evidenced by an increase in the number of leukocytes in the spinal fluid and an occasional headache.

Convulsive Seizures Due to Penicillin Acting Directly on the Cerebral Cortex and the Cerebral Ventricle.—Walker and Johnson [373] investigated the effect of penicillin applied directly to the cerebral cortex in 11 monkeys and 19 cats, because of a case in which intraventricular injection caused convulsive seizures.[374]

Their conclusions [373] are: [1] "A considerably larger dose of penicillin [than the threshold convulsive dose for cats, which is 1,000 to 2,000 Oxford units] may be injected intracerebrally or intraventricularly into human beings without producing convulsive manifestations. . . . [2] Injected near the motor area, . . . 10,000 Oxford units has given rise to twitchings of the face and hands for three hours. [3] Since the full therapeutic effect of penicillin may be obtained with doses of 20,000

372. Rammelkamp, C. H., and Keefer, C. S.: The Absorption, Excretion and Toxicity of Penicillin Administered by Intrathecal Injection, Am. J. M. Sc. **205**: 342-350 (March) 1943.

373. Walker, A. E., and Johnson, H. C.: Convulsive Factor in Commercial Penicillin, Arch. Surg. **50**:69-73 (Feb.) 1945.

374. Johnson, H. C., and Walker, A. E.: Intraventricular Penicillin: A Note of Warning, J. A. M. A. **127**:217-219 (Jan. 27) 1945.

units or less, it seems improbable that advantages of this drug will be marred by its convulsive factor, . . ." especially when used in "abscess cavities, the inflammatory linings of which impair diffusion of the penicillin. . . . [4] However, the amount of penicillin injected into the cisterna magna and the cerebral ventricles may well be limited by the convulsive factor."

According to Rammelkamp,[375] "Penicillin . . . is soluble in body fluids and is relatively non-toxic. . . . penicillin is excreted rapidly in the urine, . . . After parenteral administration penicillin diffuses poorly so that high concentrations frequently cannot be obtained at the site of the infection. Once the concentration is sufficient, an antibacterial effect is produced. The effect is not dependent on phagocytosis, and, . . . is not inhibited by substances in the body."

In meningitis penicillin does not penetrate the subarachnoid space in appreciable amounts, so that it is necessary to inject penicillin into the subarachnoid space or intracisternally in order to produce the desired effect. Ten thousand units diluted in isotonic solution of sodium chloride in a concentration of 1,000 units per cubic centimeter should be injected once or twice daily, depending on the clinical course and the presence of organisms.[376]

In certain cases Spurling prefers that penicillin be injected into the lateral ventricles through a burr hole rather than intraspinally, in order to insure better diffusion of the drug from above downward, but the intraspinal injection is also employed.[377]

15 Lombardy Street.

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375. Rammelkamp, C. H.: Mode of Action of Gramicidin and Penicillin in the Treatment of Infections, J. Bact. **45**:66 (Jan.) 1943. Rammelkamp and Keefer.[372]

376. Merck's Story of Penicillin.

377. Colbert, R. M.: Osteomyelitis of the Frontal Bone Treated with Penicillin, Ann. Otol., Rhin. & Laryng. **53**:522-530 (Sept.) 1944.

News and Comment

FIRST PAN-AMERICAN CONGRESS OF OTORHINOLARYNGOLOGY AND BRONCHO-ESOPHAGOLOGY

A meeting of this society will be held in Chicago in October 1946, sponsored by the American Academy of Ophthalmology and Otolaryngology, with the cooperation of the societies of otorhinolaryngology of the other American republics and Canada. It will follow immediately after, and overlap, the annual meeting of the American Academy of Ophthalmology and Otolaryngology. Those attending the Pan-American Congress from other countries will be invited to participate as guests in the scientific and social activities of the meeting of the Academy. All otorhinolaryngologists of good standing in North, Central and South America and the West Indies are invited to attend.

Transportation and Hotel Accommodations; Registration.—The Pan-American Airways and connecting railways, as well as railroad and steamship lines, will be requested to allow discounts on fares for those attending the Congress.

Every effort will be made to secure hotel accommodations in Chicago, provided reservations are made long enough in advance.

The registration fee for the Pan-American Congress will be $5.

Those wishing to attend the Congress are requested to communicate immediately with the Secretary. Titles for papers or motion picture films in any of the four official languages, Spanish, Portuguese, French and English, are solicited by the Program Committee.

CHEVALIER L. JACKSON, Secretary,
Pan-American Congress of Oto-Rhino-Laryngology
and Broncho-Esophagology
255 South 17th Street
Philadelphia 3, Pa., U. S. A.

EXAMINATION FOR CERTIFICATION OF SPECIALISTS

The American Board of Otolaryngology will conduct an examination in Chicago at the Palmer House on Oct. 8 to 12, 1946.

Abstracts from Current Literature

Ear

War Injuries to the Auditory Apparatus: Clinical and Audiometric Observation. M. M. Hipskind, Laryngoscope **55**:678 (Dec.) 1945.

Injuries of the hearing apparatus occurred in many of the war casualties (5.8 per cent of those admitted to one hospital). The methods of examination and classification are given. Those exposed to combat noise showed a threshold dip at 4,096 double vibrations. The reason for this has not been well determined. They also usually showed more loss of the high tones than of the low tones. The group with hearing loss not associated with combat noise showed no dip at 4,096 and no greater loss of the high tones.

Battle noises produce the same effects on those with previous hearing impairment as on those without.

Patients complaining mostly of tinnitus showed a high tone loss, maximal at 11,584 double vibrations.

There were many with functional deafness: hysterical and simulated. The hysterical group gave no responses to tests except the cold caloric test; the response to this was normal. Many of those with simulated deafness were discovered by the Stenger test. The author developed another test for this condition, which he called the "Real Life Test" (described in the article).

A "schematic representation of the incidence of shell, mine and other explosions in terms of distance and location" is given. There were more left-sided than right-sided involvements, probably due to temporary deafness of the left ear from the muzzle blast of the soldier's own gun. Traumatic perforations of the ear drums were discussed.

Hitschler, Philadelphia.

Temporary Deafness Following Exposure to Loud Tones and Noise. H. Davis, C. T. Morgan, J. E. Hawkins Jr. Galambos and F. W. Smith, Laryngoscope **56**:19 (Jan.) 1946.

The ears of 15 people were exposed to intense tones (110 to 130 decibels) of different frequencies and also to a continuous frequency spectrum for varying lengths of time (one to sixty-four minutes). The loss of hearing produced by such exposure was measured in several ways.

Some of the authors' conclusions follow. There was no evidence of cumulative injurious effects. The loss occurred at frequencies above those used in the test. The higher frequencies produced more loss. Most of the loss occurred during the first minute of exposure. The loss is of the "nerve deafness" type. Certain pure tone exposures produced diplacusis. Impairment of understanding of speech is more closely related to the overall loudness loss at the intensity level at which speech is heard than to the threshold loss shown in the audiogram or to the loudness loss in any special portion of the speech frequency range.

The authors emphasize that "the audiogram alone is not an adequate measure of the impairment of the auditory function."

Hitschler, Philadelphia.

Effect of Blast on the Human Ear. F. Boyes Korkis, Brit. M. J. **1**:198 (Feb. 9) 1946.

Korkis presents an interesting study of blast injuries of the ear as seen first hand in base hospitals in the Middle East and in Italy. Of 1,000 consecutive battle casualties, 31 (3.1 per cent) had deafness attributable to blast. The ratio of ruptured to nonruptured drums was 1:2; however, the greater injury to the

hearing apparatus by far occurred in those ears where no drum rupture was present. The injury was both direct, caused by the blast wave, with a positive and a negative phase, and indirect, as in skull fracture. Various symptoms are outlined clearly in the groups of cases comprising the middle ear type and the inner ear type; the deafness was usually worse in the inner ear type, whereas vertigo, otalgia, headache and bleeding were more prominent in the middle ear type; also there was more otorrhea in the latter.

Typical audiograms of the middle ear type showed a drop to the left; those of the inner ear type, a drop to the right.

The most common complication was chronic otitis media; mastoiditis was uncommon.

In general, the response to chemotherapy was excellent. Penicillin was not used. Thirty grams of a sulfonamide drug was given over a period of a few days if otorrhea persisted for fourteen days.

The prognosis was good if the patient was treated in a hospital, both as to otorrhea and as to repair of the drum, also as to improvement in hearing, though little could be done for those having nerve deafness. The average time spent in the hospital was eighteen days.

As prophylaxis, the wearing of suitable ear plugs and frequent testing of hearing are recommended.

As far as prognosis is concerned, the drums usually heal well, though some conduction deafness remains in those whose drums were ruptured and whose otorrhea has persisted; a few continue to have high grade inner ear deafness. In general it may be said that any deafness remaining at the end of six months is likely to be permanent.

In summation one might say that there is a high percentage of cochlear trauma in patients who have undergone blast ruptures; infection occurs after rupture in about half the patients and usually begins within four days after the injury. The prognosis is doubtful and should be guarded.

LIEBERMAN, Philadelphia.

CONSERVATIVE TREATMENT OF SUPPURATIVE OTITIS MEDIA. R. SCOTT STEVENSON and J. CHALMERS BALLANTYNE, J. Laryng. & Otol. **60**:166 (April) 1945.

Stevenson and Ballantyne report 32 cases of chronic suppurative otitis media treated by the "dry method."

In 18 cases powdered sulfathiazole ascorbate, an equimolar mixture of amorphous sulfathiazole and ascorbic acid, was insufflated after a careful toilet of the ear had been performed. The process was repeated daily until the ear was dry. In all cases the ear was dry after from one to five treatments, the average being 2. The treated ear remained dry during the observation period of from seventy-two to one hundred and sixty-one days. In 8 cases the perforation of the tympanic membrane completely healed.

In 14 cases a powder of amorphous sulfathiazole plus the sodium salt of penicillin containing 500 Oxford units of sodium penicillin per gram of sulfathiazole was used in the manner outlined in the foregoing paragraph. Results were not as gratifying as when sulfathiazole ascorbate was used, and it was felt that the instability of the sodium penicillin was responsible for the poor results, somewhat longer periods of treatment being required on the average, and suppuration continuing in 1 case after treatment. In 4 cases the perforations healed. The authors express hope that a powder of sulfamezathine plus the calcium salt of penicillin (5,000 Oxford units per gram) will prove more satisfactory.

Two cases in which the otitis was treated with zinc ionization are reported, the authors expressing the opinion that if dry methods fail to produce cessation of suppuration after one month of careful treatment, one should resort to ionization. Failing this, conservative treatment should give way to radical surgical operation.

LEJEUNE and STEELE.

Pharynx

THE USE OF PENICILLIN IN VINCENT'S ANGINA. PAUL L. SHALLENBERGER, EARL R. DENNY and HAROLD PYLE, J. A. M. A. **128**:706 (July 7) 1945.

For 13 patients suffering from Vincent's angina who were treated with oxidizing agents (silver nitrate or oxyphenarsine hydrochloride), the average time before negative smears were obtained was 8.8 days. For 11 patients treated with sulfadiazine lozenges, given every 4 hours, the time was 7.1 days. For 9 patients given local applications of penicillin solution, 250 to 500 units per cubic centimeter four times daily, the time was 3.7 days. This excluded 1 patient who, although clinically cured, had a positive smear on the eleventh day. For 2 severely ill patients given penicillin intramuscularly, 15,000 units every 3 hours, the time was reduced to 11 hours.

BAIRD, Wauwatosa, Wis. [AM. J. DIS. CHILD.]

ORAL PENICILLIN. MAXWELL FINLAND, MANSON MEADS and EDWIN M. ORY, J. A. M. A. **129**:315 (Sept. 29) 1945.

Oral administration of 90,000 units of penicillin one-half hour before breakfast gave blood levels comparable to those obtained with intramuscular injection of 15,000 to 20,000 units. Postprandial oral administration gave irregular results. Gastric achlorhydria resulted in higher levels before a meal and higher and better levels postprandially.

Various methods of administration were tried, all without untoward effect, except in the case of 1 capsule, which caused abdominal distress and increased peristalsis probably due to an ingredient other than penicillin. The serum levels obtained with the administration of ordinary commercial penicillin powder in isotonic solution of sodium chloride were at least as high and as sustained as those obtained with any other method, except that combination with aluminum hydroxide gel U. S. P. gave slightly better results after meals.

Effective blood levels of penicillin could be maintained by oral administration of doses of 90,000 to 100,000 units every two hours. Preliminary studies indicate good results of the treatment of gonorrhea and pneumococcic pneumonia and suggest that oral administration is feasible in the treatment of infections known to respond to relatively low doses of parenterally administered penicillin.

BAIRD, Wauwatosa, Wis. [AM. J. DIS. CHILD.]

Miscellaneous

STUDIES ON THE STREPTOCOCCI ("ENTEROCOCCI") OF LANCEFIELD GROUP D: II. RECOVERY OF LANCEFIELD GROUP D STREPTOCOCCI FROM ANTE-MORTEM AND POSTMORTEM CULTURES FROM INFANTS AND YOUNG CHILDREN. S. M. WHEELER and G. E. FOLEY, Am. J. Dis. Child. **70**:207 (Oct.) 1945.

It is regrettable that Dr. Wheeler was killed in action on April 13, 1945! These studies were made at the Harvard Medical School and School of Public Health, Department of Medicine and Epidemiology. This is essentially a research in bacteriology and is full of technical details. Cultures were taken from the noses, the throats and the rectums of babies in the spring of 1941 and later, when they were suffering from "purulent rhinitis," which more accurately is acute purulent sinusitis. Beta streptococci were predominant but were not heat resistant, and were killed by pasteurization or, at least, deactivated. The infection was air borne or transmitted on contact. Some patients had associated diarrhea (swallowed organisms). Strains isolated from adults established that group D streptococci (especially those with the beta reaction on blood agar) are seldom present. At autopsies on 73 infants who died from various causes 94 strains of streptococci were isolated. Of these, 65 per cent belonged to Lancefield group D. Staphylococcus aureus was encountered frequently but not always. Twenty-eight strains of streptococci were isolated from cases of fulminating infection. Alpha, beta and

gamma strains were encountered in all serologic types of group D streptococci. Most strains were avirulent for mice, and only 10 per cent were resistant to heat. Biochemical characteristics were of no value in the recognition of the various serologic types.

VOORHEES, New York.

CILIA AND PENICILLIN. ARTHUR W. PROETZ, Ann. Otol., Rhin. & Laryng. **54**:94 (March) 1945.

Through his experiments with the cilia of the rabbit's trachea, Proetz has demonstrated that penicillin (the sodium salt) in isotonic solution of sodium chloride when locally applied in the strength recommended for local application (250 units per cubic centimeter) in no way affected the ciliary beat. When a solution containing 500 units per cubic centimeter was used, the beat was less vigorous and the active period was shortened to eighteen hours (average). (With the 250 unit strength the beat ceased only when the epithelium disintegrated, which it did in all specimens, even the controls, after some twenty-seven hours.) With solutions containing 5,000 units per cubic centimeter the beat was reduced to approximately half speed within a few minutes and this speed was observed until the cilia stopped beating, in three and a half to six and a half hours, without any sign of surface disintegration.

M. V. MILLER, Philadelphia.

PLASTIC REPAIR FOR PROTRUDING EARS. M. I. BERSON, Eye, Ear, Nose & Throat Monthly **24**:423 (Sept.) 1945.

Berson emphasizes the emotional effect of protruding ears on children. The shape of the ear is fully formed at 5 years of age, and operation thereafter will not interfere with later growth. Protruding ears are usually congenital. The author repositions the ear by constructing an anthelix, which is lacking. This reduces the distance between the concha and the cuticular margin, as well as the angle between the concha and the side of the head, which is normally 30 degrees. The exact position finally desired for the ears is carefully marked on the skin where the ear should rest against the head. This should be done with the patient in the upright position and before the injection of a local anesthetic agent, since this may shrink the skin. The entire anterior and posterior portions of the proposed field are anesthetized with monocaine hydrochloride 1.5 per cent and epinephrine hydrochloride 1: 100,000. This is introduced with a 2 inch, 22 gage needle between the skin and the cartilage of the ear and is expressed as the needle is withdrawn slowly and under light pressure. The elliptic section of the skin, already marked, is excised with a small scalpel, and an elliptic portion of the underlying cartilage is resected, care being taken that the skin on the anterior surface is not perforated. By beveling the edges of the cartilages to be approximated, an anthelix is formed. If the removal of cartilage results in the formation of folds of skin on the anterior surface of the ear, these can be reduced by wide undermining of the skin. The margins of cartilage are joined by mattress sutures and the skin is approximated with fine interrupted silk sutures. Gauze impregnated with 5 per cent sulfathiazole ointment is applied to the back of the ear, and moist gauze is pressed into the anterior convolutions of the ear. The dressings are kept in place by a firm dressing for seven days, when the sutures are removed.

SELTZER, Philadelphia.

THERAPEUTIC EFFECTIVENESS OF PENICILLIN IN THE TREATMENT OF VINCENT'S STOMATITIS AND ITS FAILURE TO INFLUENCE FAVORABLY CERTAIN OTHER MEDICAL CONDITIONS. JAMES S. SWEENEY, WILLIAM J. MORGINSON, ROGER W. ROBINSON and ELMER M. KILPATRICK, J. Lab. & Clin. Med. **30**:132 (Feb.) 1945.

Forty-three patients with Vincent's stomatitis were treated with the antibiotic penicillin, with good results. The penicillin was administered intramuscularly in

doses of 25,000 units at three hour intervals. After forty-eight hours it was impossible to find fusiform bacilli or spirochetes except in patients in whom dental caries was present. These organisms rapidly disappeared after dental prophylaxis. There was an increase in temperature from 99.1 to 101 F. during the time the penicillin was administered. The results obtained from the use of penicillin in other conditions were as follows:

1. In 3 cases of chronic recurring furunculosis the treatment was regarded only as palliative or as a temporary adjunct, for there were recurrences.

2. In 11 cases of acne vulgaris there were some signs of improvement, but none of the patients were cured and there was no decided improvement.

3. In 7 cases of staphylococcic dermatitis there was some evidence of improvement, but relapse was frequent.

4. In 7 cases of asthma due to various strains of staphylococci and streptococci recovered from the paranasal sinuses there was some initial improvement, but it was not sustained.

5. In 5 cases of malaria there was no improvement from the treatment. However, the patients when subsequently treated with small doses of antimalarial agents responded promptly. There were no recurrences of malaria at the end of six months.

6. In 2 cases of subacute bacterial endocarditis the cultures of the blood became sterile during the treatment, but they became positive for pathogens after the treatment was stopped.

7. In 1 case of acute disseminated lupus erythematosus there was no clinical improvement at any time during the treatment.

8. One or more patients with the following diseases failed to respond to the administration of penicillin: chronic pyelonephritis; aerobic and anaerobic nonhemolytic streptococcus infections; diphtheria; mumps; eczema; folliculitis; dermatitis herpetiformis; acute myeloid leukemia; follicular lymphoblastoma (Brill-Symmer disease). There were several patients with trichophytosis who showed no improvement during the administration of penicillin. Three patients showed mild to moderate urticarial reaction from the treatment; this disappeared within a few days during the period of penicillin therapy.

GELBER, Los Angeles. [AM. J. DIS. CHILD.]

THE ADMINISTRATION OF PENICILLIN BY CONTINUOUS INTRAMUSCULAR DRIP. R. O. SMITH and C. G. HARFORD, J. Lab. & Clin. Med. **30**:502 (June) 1945.

This report indicates that the continuous intramuscular administration of penicillin affords a practical method of maintaining relatively high concentrations of penicillin in the blood; the blood levels are approximately the same as those reported when the drug is administered by continuous intravenous drip. However, in more than half of the patients studied, local reactions developed at the sites of the continuous intramuscular injections; this complication would seem to be too frequent to warrant routine use of this method. It is suggested that if more highly purified preparations of penicillin fail to cause local reactions, the method of continuous intramuscular administration may be justifiably retained.

WILKINSON, Galveston, Texas. [AM. J. DIS. CHILD.]

HEREDITARY HEMORRHAGIC TELANGIECTASIA: AN ANALYSIS OF CAPILLARY HEREDOPATHIES. KARL SINGER and W. Q. WOLFSON, New England J. Med. **230**:637 (May 25) 1944.

A family presenting hereditary hemorrhagic telangiectasia, together with a positive reaction to a tourniquet test, is described. Pseudohemophilia is characterized by a prolonged bleeding time but no reaction to a tourniquet test, and hereditary purpura simplex, by a normal bleeding time but a positive reaction to a tourniquet test. Combinations of both types occur.

Hereditary hemorrhagic telangiectasia is a localized gross abnormality of capillaries, usually not accompanied with any systemic capillary dysfunction. The observed family presents, however, such a combination of localized gross deviation of capillary structure and increased capillary fragility.

GENGENBACH, Denver. [AM. J. DIS. CHILD.]

TUMORS OF THE CEREBELLOPONTILE ANGLE. E. SALGADO BENAVIDES, Arch. Soc. oftal. hispano-am. **4**:75 (Jan.-Feb.) 1944.

After an extensive discussion of the neurologic symptoms and ocular signs associated with tumors of the cerebellopontile angle, the author arrives at the following conclusions:

In the present state of knowledge the ophthalmologist cannot with certainty contribute to the differentiation of neuroma of the acoustic nerve and other tumors of the cerebellopontile angle. Cranial hypertension produces a series of changes in the fundus oculi, of which papilledema is the typical one. Paralysis of the sixth nerve, of frequent occurrence, has little localizing value. It may be evidence of intracranial hypertension, or it may be produced by tumor tissue infiltrating the nucleus of the nerve or by pressure on the nerve root, which has a long course. The homolateral loss of the corneal reflex, always present with tumors of the cerebellopontile angle, is of localizing value, since it makes its appearance early as a sign of involvement of the trigeminal nerve.

CARRASQUILLO. [ARCH. OPHTH.]

PNEUMOCOCCIC MENINGITIS. ADOLFO COLOMBO, Rev. Soc. pediat. d. litoral **10**:3 (Jan.-April) 1945.

Before the period of therapy with sulfonamide compounds the mortality resulting from this disease was 95 per cent. Sulfonamide drugs have reduced the mortality to 53 per cent. The combination of penicillin with sulfonamide drugs will probably reduce the mortality to far below this figure. A case report is given of a boy 11 years old, who was hospitalized four days after the onset of purulent pneumococcic meningitis. Treatment with sulfonamide compounds alone (sulfathiazole and sulfamerazine) brought about little improvement. Combined treatment — Soluseptazine (4-sulfonamidophenyl-gamma-disulfonic acid) administered intrathecally, plus penicillin, administered intramuscularly (300,000 units)—resulted in immediate improvement and quick recovery.

The author feels that it would have been preferable to administer the penicillin intrathecally. However, the striking success in this case seems to disprove the theory that the meninges present a definite barrier to penicillin. Possibly, the permeability is greater from the blood to the spinal fluid than in the opposite direction. Furthermore, permeability probably is increased when inflammatory processes are present. According to experimental studies, penicillin and sulfonamide compounds are true synergists: The bacteriostatic power of penicillin is more than doubled in the presence of sulfonamide compounds. Therefore, the treatment of choice in pneumococcic meningitis is a combination of sulfonamide compounds and penicillin. The intrathecal administration of penicillin is preferable, although the intramuscular or the intravenous way is effective too.

SOLMITZ, Chicago. [AM. J. DIS. CHILD.]

PULMONARY ABSCESS IN A BABY TREATED WITH PENICILLIN. L. CHIODIN and L. PRUSS, Rev. Soc. pediat. d. litoral **10**:13 (Jan.-April) 1945.

A baby 28 months old was treated for pulmonary abscess with different drugs, including sulfathiazole, for a month without improvement. After five days of treatment with penicillin there was complete recovery. Instructive roentgenograms are included.

SOLMITZ, Chicago. [AM. J. DIS. CHILD.]

Directory of Otolaryngologic Societies *

INTERNATIONAL

First Pan-American Congress of Oto-Rhino-Laryngology and Bronchoesophagology

President: Dr. Gordon B. New, Mayo Clinic, Rochester, Minn.
Secretary: Dr. Chevalier L. Jackson, 255 S. 17th St., Philadelphia 3.
Place: Palmer House, Chicago. Time: Oct. 17-19, 1946.

NATIONAL

American Medical Association, Scientific Assembly, Section on Laryngology, Otology and Rhinology

Chairman: Dr. Louis H. Clerf, 1530 Locust St., Philadelphia.
Secretary: Dr. Fletcher D. Woodward, 104 E. Market St., Charlottesville, Va.

American Academy of Ophthalmology and Otolaryngology

President: Dr. Gordon B. New, Mayo Clinic, Rochester, Minn.
President-Elect: Dr. Alan C. Woods, Johns Hopkins Hospital, Baltimore 5.
Executive Secretary-Treasurer: Dr. William L. Benedict, 100–1st Ave. Bldg., Rochester, Minn.
Place: Palmer House, Chicago. Time: Oct. 13-18, 1946.

American Broncho-Esophagological Association

President: Dr. Robert M. Lukens, 1923 Spruce St., Philadelphia.
Secretary: Dr. Paul Holinger, 700 N. Michigan Ave., Chicago 11.

American Laryngological Association

President: Dr. Frank R. Spencer, Physicians Bldg., Boulder, Colo.
Secretary: Dr. Arthur W. Proetz, Beaumont Bldg., St. Louis.

American Laryngological, Rhinological and Otological Society, Inc.

President: Dr. Harry W. Lyman, 906 Carleton Bldg., St. Louis.
Secretary: Dr. C. Stewart Nash, 708 Medical Arts Bldg., Rochester 7, N. Y.

SECTIONS:

Eastern.—Chairman: Dr. Robert F. Ridpath, 18th and Chestnut Sts., Philadelphia.
Southern.—Chairman: Dr. Walter T. Hotchkiss, 541 Lincoln Rd., Miami Beach, Fla.
Middle.—Chairman: Dr. Oliver E. Van Alyea, 135 S. La Salle St., Chicago.
Western.—Chairman: Dr. Colby Hall, 1136 W. 6th St., Los Angeles, Calif.

American Otological Society

President: Dr. William E. Grove, 324 E. Wisconsin Ave., Milwaukee, Wis.
Secretary: Dr. Gordon D. Hoople, 713 E. Genesee St., Syracuse, N. Y.

American Otorhinologic Society for the Advancement of Plastic and Reconstructive Surgery, Inc.

President: Dr. Alfred Schattner, 115 E. 61st St., New York.
Secretary: Dr. Norman N. Smith, 291 Whitney Ave., New Haven, Conn.
Place: New York. Time: Nov. 14, 1946.

* Secretaries of societies are requested to furnish the information necessary to keep this list up to date.